FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF ACECLOFENAC USING DIFFERENT POLYMERS

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MASTER OF PHARMACY

(Pharmaceutics)

Submitted by

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MELMARUVATHUR - 603 319

MAY- 2012

CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF ACECLOFENAC USING DIFFERENT POLYMERS**" submitted to The Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by **M. MANIYARASI (Register No. 26106005)** in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2011-2012.

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CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF ACECLOFENAC USING DIFFERENT POLYMERS**" the bonafide research work carried out by **M. MANIYARASI (Register No. 26106005)** in the Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University under the guidance of **Dr. S. SHANMUGAM, M. Pharm., Ph.D.** Professor, Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur.

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Dedicated

to

My parents

&

Friends

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ABBREVIATION AND MEANING

%	-	Percentage
%DE	-	Percentage dissolution efficiency
µ	-	Micron
µg/ml	-	Microgram per millilitre
^{0}C	-	Degree celsius
LAM	-	Lamivudine
Cm^{-1}	-	Centimeter inverse
C_{max}	-	Peak plasma concentration
DNA	-	Deoxy ribonucleic acid
DSC	-	Differential scanning calorimetry
e.g.	-	Example
EC	-	Ethyl cellulose
edn	-	Edition
F	-	Formulation
F/C	-	Film coated
FTIR	-	Fourier transform infrared spectroscopy
g/ml	-	gram per millilitre
GIT	-	Gastro intestinal tract
HCl	-	Hydrochloric acid
HPC	-	Hydroxypropyl cellulose

HPMC	-	Hydroxypropyl methylcellulose
hrs	-	Hours
ICH	-	International conference on harmonization
IP	-	Indian pharmacopoeia
Kg/cm^2	-	kilogram per centimeter square
LBD	-	Loose bulk density
MDT	-	Mean dissolution time
mg	-	milligram
ml	-	millilitre
ml/min	-	millilitre per minute
mm	-	millimeter
N	-	Normality
NaOH	-	Sodium hydroxide
NF	-	National formulary
nm	-	nanometer
^{o}	-	Degree
pH	-	Negative logarithm of hydrogen ion
pKa	-	Dissociation constant

qs	-	Quantity sufficient
RH	-	Relative humidity
rpm	-	Revolution per minute
S.No.	-	Serial number
SD	-	Standard deviation
SR	-	Sustained release
$t_{1/2}$	-	Biological half life
TBD	-	Tapped bulk density
T_{max}	-	Time of peak concentration
USP	-	United states pharmacopoeia
UV	-	Ultraviolet
w/w	-	weight per weight
λ_{max}	-	Absorption maximum

Introduction

1.INTRODUCTION

1.1. Oral drug delivery system: *(Banker G.S and Rhodes C.T., 2009; Chein Y.W., 2002)*

An ideal drug delivery system should aid in the optimization of drug therapy by delivering an appropriate amount to the intended site and at a desired rate. Hence, the DDS should deliver the drug at a rate dictated by the needs of the body over the period of treatment. An oral drug delivery system providing a uniform drug delivery can only partly satisfy therapeutic and biopharmaceutical needs, as it doesn't take in to account the site specific absorption rates within the gastrointestinal tract (GIT). Therefore there is a need of developing drug delivery system that release the drug at the right time, at the specific site and with the desired rate.

1.2. Drawbacks associated with conventional dosage forms: *(Brahmankar D.M. and Jaiswal S.B., 2009; http://www.pharmainfo.net)*

1. A drug with short biological half life which needs a close succession administration is required, so it may increase the missing of dosage form leads to Poor patient compliance.

2. The uncontrollable fluctuation of drug level may leads to either below effective range or over the effective range.

3. Plasma concentration verses time profile of dosage form and it's difficult to achieve the steady state active drug level.

4. The rise and fall of drug levels it may give to accumulation of adverse effects especially for a drug having less therapeutic index.

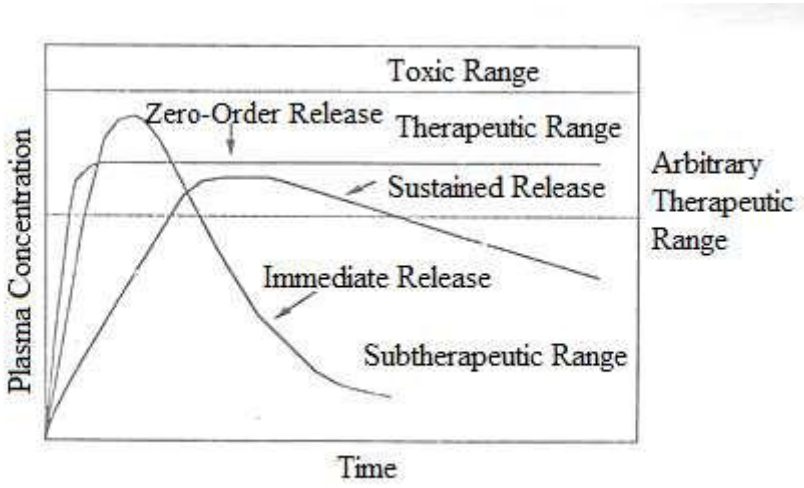


Figure 1.1: Plasma drug concentration profiles for conventional tablet formulation, a sustained release formulation and a zero order controlled release formulation.

1.3. Sustained release drug delivery system: *(Banker G.S. and Rhodes C.T., 2009; Shargel L. and Andrew B.C.Y., 2005; Aulton M.E., 2007; Ansel H.C., 2009; Brahmankar D.M. and Jaiswal S.B., 2009)*

The main destination of any drug delivery system is to furnish a contributing to quantity of a drug to a suitable region in the body and that the required drug concentration can be attained promptly and then being maintained. The drug delivery system should distribute a drug at a rate dictated by the require of the body for particular length of time. Regarding this existing points there are two important aspects to delivery system, said as, spatial placement and temporal delivery. Spatial placement connected to targeting a drug to particular organ, tissues, cells, or even sub cellular area; whereas temporal delivery system deals to controlling the rate of dosage form to the targeting region.

Sustained release tablets and capsules are mostly taken only once or twice daily, compared with immediate release tablet form that may have to take 3 or 4 times

a day to attain the same required drug to produce the effect. Typically, the sustained release dosage form to furnish at once release the active component that give the what we are desired for cure of disease, followed by remaining quantity of drug should be release and maintained the therapeutic effect over a predetermined length time or prolonged period. The sustaining of drug plasma levels furnish by sustained release dose often times to eliminate the require for night dose administration, which suitable not only the patient but the care given as well.

The bulk of research can be focusing toward oral dosages that improve the temporal aspect of drug delivery. This approach is a continuously developing in the pharmaceutical industry for sustained release oral drug delivery system.

The sustained release system for oral use of administration are mostly solid and based on dissolution, diffusion or a combination of both, erosion mechanisms, in the power to directing the drug release. A delivery system containing hydrophilic and hydrophobic polymers and waxes are mixed with active component to furnish drug action for a prolonged length of time.

The concept of modified release dosage products was previously used to describe various types of oral extended release dosage forms, including sustained release, sustained action, prolonged action, slow release, long action and retarded release.

The USP/NF associated with several types of modified-release dosage forms,

1. Extended release dosage forms. (e.g. sustained release dosage forms, controlled release dosage forms)
2. Delayed release dosage forms (e.g. enteric coated tablets)
3. Targeted release dosage forms.

The **United States Pharmacopoeia** has been in the term **extended release** and the **British Pharmacopoeia** has been the term **slow release**. **United States Food and Drug Administration** has been in the term **prolonged release**. However the review of literature indicates that widely used in terms today are sustained release and controlled release.

Modified release dosage forms: It is a dosage form are defined by the USP as those whose drug release characteristics of time course or location are chosen to accomplish therapeutic or convenience objective not offered by conventional or immediate release form. Also this dosage form which is sufficiently controlled to provide periods of prolonged therapeutic action following each administration of a single dose.

Extended release dosage form: It is a dosage forms release drug slowly, so that plasma concentration is maintained at a therapeutic level for a period of time.

Delayed release dosage form: It is a dosage form which indicates that the drug is not being released immediately following administration but at a later time, e.g. enteric coated tablets.

Prolonged release dosage form: It is a dosage form which indicates that the drug is provided for absorption over a longer period of time than from a conventional dosage form.

Sustained release dosage form: It is a dosage form which indicates an initial release of drug sufficient to provide a therapeutic amount dose soon after administration, and then a gradual release over an extended period of time.

1.3.1. Advantages of sustained release drug delivery system: *(Banker G.S and Rhodes C.T., 2009; Chein Y.W., 2002)*

Some advantages are as follows

1. Reduction in dosing frequency.
2. Reduced fluctuation in circulating drug levels.
3. Increased patient convenience and compliance.
4. Avoidance of night time dosing.
5. More uniform effect.
6. Maximum utilization of drug.
7. Reduction in GI irritation and other side effects.
8. Reduction in health care cost through improved therapy.
9. Improve bioavailability of some drugs.

1.3.2. Disadvantages of sustained release drug delivery system: (*Banker G.S. and Rhodes C.T., 2009; Chein Y.W., 2002)*

1. Decreased systemic availability in comparison to immediate release conventional dosage form. This may be due to
   - Incomplete release
   - Increased first-pass metabolism, increased instability
   - Site specific absorption, pH dependant solubility, etc.
2. Poor *in vitro-in vivo* correlation.
3. Possibility of dose dumping.
4. Retrival of drug is difficult in case of toxicity, poisoning, or hypersensitivity reactions.
5. Higher cost of formulation.

1.3.3. Rationale of sustained release drug delivery system:

(http://www.pharmainfo.net; Chein Y.W., 2002)

The basic rationale for sustained drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration. It is desirable that the duration of drug action become more to design properly. Rate controlled dosage form, and less, or not at all, a property of the drug molecules inherent kinetic properties.

As mentioned earlier, primary objectives of controlled drug delivery are to ensure safety and to improve efficiency of drugs as well as patient compliance. This achieved by better control of plasma drug levels and frequent dosing. For conventional dosage forms, only the dose and dosing interval can vary and, for each drug, there exists a therapeutic window of plasma concentration, below which therapeutic effect is insufficient, and above which toxic side effects are elicited. This is often defined as the ratio of median lethal dose (LD 50) to median effective dose (ED50).

1.3.4. Design of sustained release drug delivery system: *(Jithan A., 2007; Ansel H.C., 2009; Shargel L. and Andrew B.C.Y., 2005)*

Practically there are two modern methods are mostly used by pharmaceutical manufacturing scientist in the designing of dosage form for sustained release tablet. In that the first approach method are mainly involved to modifying of properties like physical and chemical nature of the drug and the second method is how to modify the release of drug from the prepared dosage form. Physical and chemical characteristic of the active component can be developed by formatting complex type, drug and

adsorbate formulation, or prodrug synthesis. The conversion of inactive form to active nature process is mostly attempted and investigated. The second method is used in the formulation development of sustained release system. This is popular method because it's inherent advantage. The advantage of this method in the design of dosage form is independent. The final formulation form could be in a liquid suspension form, a capsule or a tablet.

Generally some important criteria could be considering in the formulation of a sustained release dosage form. Not all the drug ideal characteristic. Drugs which shown neither very slow or nor very fast rate of absorption and excretion. Drugs with very short half life that is less than 2 hours are poor candidates for sustained release because large quantities of drug required for such a formulation.

The drug should be absorbed in the gastro intestinal region. Drug manufacturing in sustained release tablet it have been good solubility in the intestinal and gastric fluid. They are administered in relatively small doses, drug with large single doses frequently are not suitable for sustained release. Sustained release dosage form mainly used in case of chronic condition than the acute condition. If the medicine need for acute condition at that we have to change the dose adjustment by physician alike that is given in sustained release form. Drug should have solubility and permeability properties. Drug with less protein binding properties. Drug should not produce local irritation.

1.4. Drug properties relevant to sustained release formulation: *(Chein Y.W., 2002; http://www.pharmainfo.net)*

The formulation of sustained release drug delivery systems, consider the some criteria such as the route of administration, type of drug delivery system, what disease to be treated, the patient, the duration of treatment and the characteristic of the drug those above mentioned factor should be considered. The pharmaceutical interest to research scientist for designing of the delivery system the following properties could be considered in the development of dosage form. These properties can be classified as follows.

A) Physicochemical properties

B) Biological properties

These properties having the greater importance in the design of the drug in the delivery system and in the body. But there is no distinction between these two categories because the biological properties of a drug as like a function of its physicochemical properties. By definition, physicochemical properties of drug that can be determined from *in vitro* study and biological properties will be those that result from Pharmacokinetic studies such as absorption, distribution, metabolism and excretion of a drug and those resulting from pharmacological experimental study**.**

A. Physicochemical factors influencing oral sustained-release dosage form design:

a) Dose size:

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5- 1.0g is considered maximal for a conventional dosage form. This also holds for sustained release dosage form.

Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.

b) Ionization, *pka* and aqueous solubility:

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the *pka* of the compound and the absorptive environment. Presenting the drug in an unchanged form is advantageous for drug permeation. Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to unchanged form. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of pH on the release process must be defined. Compounds with very low solubility (<0.01mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. So it is obvious that the solubility of the compound will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.

c) Partition Coefficient:

When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic; therefore the partition

coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds with very low partition coefficient, it is very difficult for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.

d) Drug Stability:

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state; therefore, this is the preferred composition of delivery for problem cases. For the dosage form that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial; this is also true for systems that delay release until the dosage form reaches the small intestine. Compounds that are unstable in small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation. Propentheline and probanthine are representative example of such drug.

e) Protein binding:

Its properties the drugs are binding to blood protein. The drug-Protein complex it can act as a depot for drug molecule and to release a drug for prolonged period and leads to exhibit a highly binding to plasma. The attractive forces is mainly applicable for binding are vanderwaals forces, hydrogen bonding and electrostatic

forces. If a drug molecule having hydrophobic in nature its can also increasing the binding capacity. Drugs binding to mucin it may increase absorption. e.g. quaternary ammonium compounds bound to mucin in the gastro intestinal tract.

B. Biological factors influencing oral sustained-release dosage form design:

a) Biological half life:

The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life ($t_{1/2}$). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the blood stream. Therapeutic compounds with short half-life are generally are excellent candidate for SR formulation, as this can reduce dosing frequency. In general, drugs with halflives shorter than 2 hours such as furosemide or levodopa are poor candidates for SR preparation. Compounds with long half-lives, more than 8 hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples.

b) Absorption:

Since the purpose of forming a SR product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. Thus corresponds to a minimum

apparent absorption rate constant of 0.17-0.23h^{-1} to give 80-95% over this time period. Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine. For many compounds this is not true. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, SR preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds try to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that co-administration results in sustaining effect. One such attempt is to formulate low density pellet or capsule. Another approach is that of bioadhesive materials.

c) Metabolism:

Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form.

Hence criteria for the drug to be used for formulating Sustained-Release dosage form is,

- Drug should have low half-life(<5 hrs)
- Drug should be freely soluble in water
- Drug should have larger therapeutic window
- Drug should be absorbed throughout the GIT.

Even a drug that is poorly water soluble can be formulated in SR dosage form. For the same, the solubility of the drug should be increased by the suitable system and later

on that is formulated in the SR dosage form. But during this the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

d) Distribution:

The distribution of active ingredient into body tissues and extra vascular spaces in the body is an important parameter for drug elimination kinetics model. Some parameters are using to give idea about distribution of drug. Apparent volume of distribution of active component is high it will influence the elimination of dosage form and not suitable for making sustained release tablet. The term apparent volume of distribution of a drug is mostly used to explain the distribution, including bound to the body system. The total apartment volume of distribution for a drug at steady state will be calculated by given equation.

$$V_{dss} = [(K_{12} + K_{21}) / K_{21}] V_P$$

Where,

V_{dss} = Apparent volume of distribution at study state level

K_{12} = Drug from central to peripheral compartment

K_{21} = Drug from peripheral to central compartment

V_P = Volume of central compartment

e) Side effects:

The incidence of side effect of a drug is depends on its therapeutic concentration level in blood. It can be remedy by the drug concentration level is controlled at which timing that drug exists in blood after administration. Toxic effect of a drug is expected above the maximum effective range level and fall in the

therapeutic effect if a drug below the level of minimum effective range. So the above problem we can solve by making sustained release preparation.

f) Margin of safety:

Therapeutic index of a drug is very important for either sustained or controlled release delivery system. Its value only desired the margin of safety. Therapeutic index value it has been longer means excellent for preparation of sustained release tablet. Narrow therapeutic index of some drug precise to release the active content in therapeutic safe and effective range. Some drug like cardiac glycosides that therapeutic index value is very small, so it's not used for sustained release delivery system.

Therapeutic index = TD_{50} / ED_{50}

Where,

TD_{50} - Median toxic dose

ED_{50} - Median effective dose

1.5. Design and fabrication of oral systems: *(Brahmankar D.M. and Jaiswal S.B., 2009; Robinson J.R. and Lee V.H.L., 2009; Chein Y W., 2002)*

The majority of oral controlled release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drugs into the gastrointestinal milieu. The following techniques are employed in the design and fabrication of oral sustained release dosage forms.

1. Dissolution controlled release
    - Encapsulation dissolution control
    - Matrix dissolution control

2. Diffusion controlled release

- Reservoir devices
- Matrix devices

3. Diffusion and dissolution controlled systems
4. Ion-exchange resins
5. pH - independent formulations
6. Osmotically controlled release
7. Altered density formulations

1.5.1. Dissolution controlled Systems:

Drug with a slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by rate of dissolution. This being the case, SR preparations of drugs could be made by decreasing their dissolution rate. This includes preparing appropriate salts or derivatives, coating the drug with a slowly dissolving material, or incorporating it into a tablet with a slowly dissolving carrier.

The dissolution process at steady state, is described by Noyes-Whitney equation,

$$dc/dt = K_D A(Cs-C) = D/h\ A(Cs-C)$$

Where,

dc/dt = Dissolution rate

K_D = Diffusion co-efficient

A = surface area of the dissolving solid

Cs = Saturation solubility of the solid

C = Concentration of solute in bulk solution

H = Thickness of diffusion layer

Encapsulation dissolution control

- These methods generally involve coating individual particles of drug with a slow dissolving material. The coated particles can be directly compressed into tablets as in space tabs or placed in capsules as in spansule products.
- Since the time required for dissolution of the coat is a function of thickness and aqueous solubility, sustained action can be obtained by employing a narrow or a wide spectrum of coated particles of varying thickness respectively.

Matrix dissolution control

- Those methods involve compressing the drug with a slowly dissolving carrier into a tablet form. Here the rate of drug availability is controlled by the rate of penetration of dissolution fluid into the matrix.
- This in turn can be controlled by porosity of the tablet matrix, the presence of hydrophobic additives and wettability of granule surface.

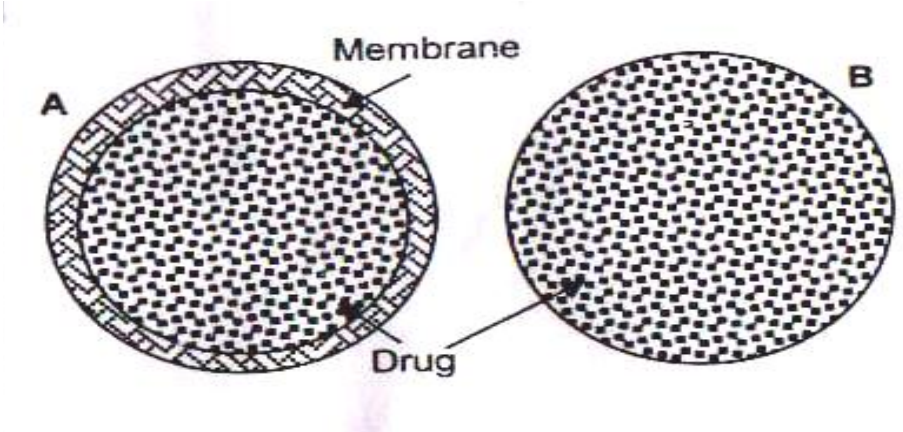


Figure 1.2: Dissolution controlled matrix system

1.5.2. Diffusion controlled systems:

Basically diffusion process shows the movement of drug molecules from a region of higher concentration to one of lower concentration. Diffusion systems are characterized by the release rate being dependent on its diffusion through an inert membrane barrier. Usually this barrier is an insoluble polymer.

Membrane reservoir diffusion controlled

The core of the drug is encapsulated within a water insoluble polymeric material. The drug will partition in to the membrane and diffuse in to the fluid surrounding the particle or tablet. Cellulose derivatives are commonly used in the reservoir types.

Ficks first law of diffusion describes the diffusion process

$$J = -D\, dc/dx$$

Where,

D = diffusion coefficient in area/time

dc/ dx = change of concentration 'c' with distance 'x'

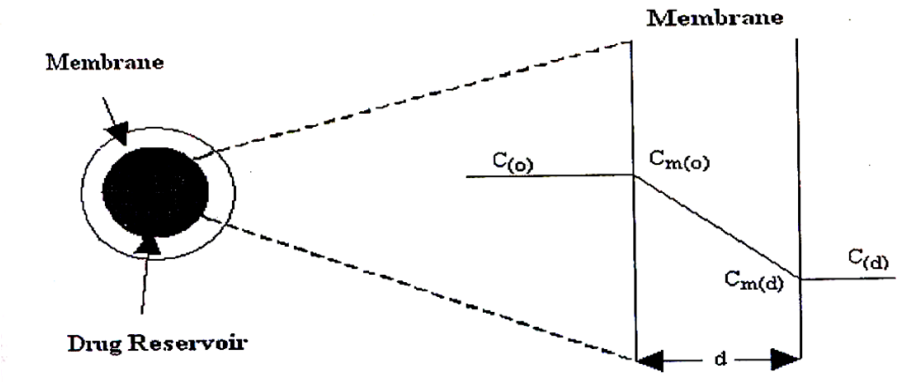


Figure 1.3: Schematic representation of reservoir diffusion controlled drug release reservoir

Advantages:

Zero order delivery is possible; release rate varies with polymer type.

Disadvantages:

1. Systems must be physically removed from implant sites.
2. Difficult to deliver high molecular weight compounds.
3. Increased cost per dosage unit, potential toxicity if system fails.

Matrix diffusion controlled:

It this system a solid drug is dispersed in an insoluble matrix. The rate of drug release is controlled by the rate of diffusion of drug and not by the rate of solid dissolution. In this model, drug in the outside layer exposed to bath solution is dissolved first and then diffuses out of the matrix. The following equation describe the rate of release of drug dispersed in an inert matrix system have been derived by Higuchi,

$$dQ/dt = (DAC_S/2t)^{1/2}$$

where

'A' is the total amount of the drug in the device,

'D' is the diffusion coefficient of the drug in the polymer, 'C_s' is the solubility of the drug in the polymer,'t' is time.

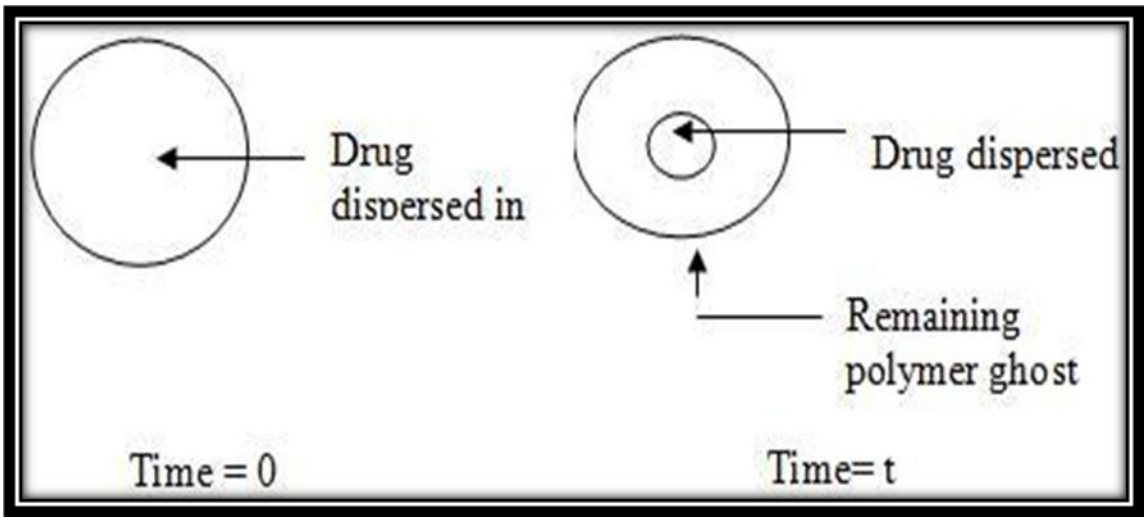


Figure 1.4: Release of drug dispersed in an inert matrix system

Advantages:

Easier to produce than reservoir or encapsulated devices, can deliver high molecular weight compounds.

Disadvantages:

Cannot provide zero order release, removal of remaining matrix is necessary for implanted system.

1.5.3. Dissolution and diffusion - controlled release system:

Normally, therapeutic systems will never be dependent on dissolution only or diffusion only. In practice, the dominant mechanism for release will over shadow other processes enough to allow classification as either dissolution rate limited or diffusion controlled.

Partially soluble membrane system

The drug is encapsulated in a partially soluble polymer (a polymer that has domains that dissolve with time). The drug diffuses through the pores in the polymer

coat. For example, a cellulose acetate and HPMC mixture is coated on to the drug particles.

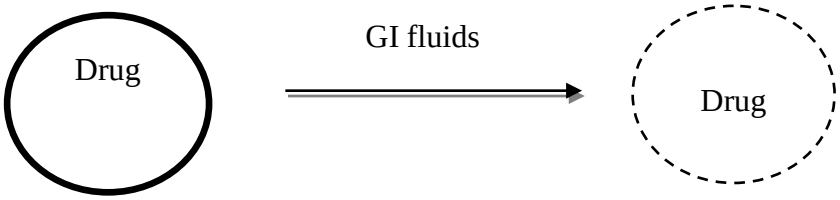


Figure 1.5: Partially soluble membrane system

Matrix system:

Matrix system encapsulate the drug in a membrane coating, where dissolution of the drug in the fluid that penetrates in to the core and diffusion of the drug from the core across the polymer membrane makes for a diffusion and dissolution controlled system.

The drug is sparingly soluble in this case, so the release rate is slow and has significant influence on the diffusion of drug across the membrane.

Advantages:

- Easier to produce than reservoir devices.
- Can deliver high – molecular weight compounds.
- Removal from implant sites is not necessary.

Disadvantages:

- Difficult to control kinetics owning to multiple process of release.
- Potential toxicity of degraded polymer.

1.5.4. Ion exchange systems:

These are salts of cationic or anionic exchange resins or insoluble complexes in which drug release results from exchange of bound drug ions that are normally present in GI fluids.

The use of ion exchange resins to prolong the effect of drugs is based on the principle that positively or negatively charged therapeutic molecules combined with appropriate resins yield insoluble poly salt resonates.

1.5.5. Osmotically controlled systems:

This device is fabricated as tablet that contains water soluble osmotically active drug, of that was blended with osmotically active diluents by coating the tablet with a cellulose triacetate barrier which functions as a semi permeable membrane. A laser is used to form a precision orifice in the barrier, through which the drug is released due to development of osmotic pressure difference across the membrane, when it is kept in water.

Advantages:

- Zero order release rates are obtainable.
- Preformulation is not required for different drugs.
- Release of drug is independent of the environment of the system.

Disadvantages:

- System can be much more expensive than conventional counter parts.
- Quality control is more extensive than most conventional tablets.

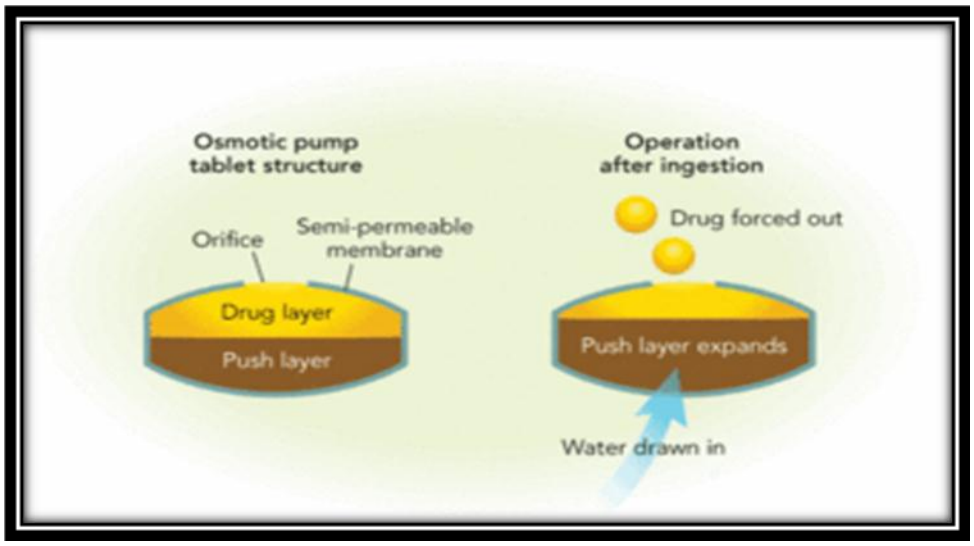


Figure 1.6: Osmotically controlled systems

1.5.6. pH independent formulations:

A buffered controlled release formulation is prepared by mixing a basic or acidic drug with or more buffering agents, granulating with appropriate pharmaceutical excipients and coating with GI fluid permeable film forming polymer. When GI fluid permeates through the membrane the buffering agent adjusts the fluid inside to suitable constant pH thereby rendering a constant rate of drug release.

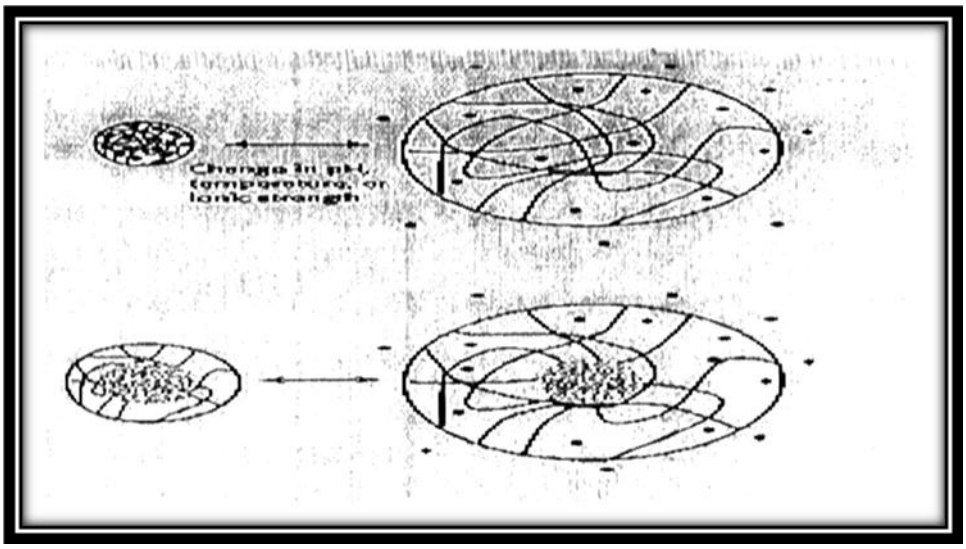


Figure 1.7: Drug delivery from environmentally pH sensitive release systems

1.5.7. Altered density formulations:

Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.

High-density approach

Low-density approach

1.6. Matrix tablets:

(Vyas S.P.and Khar R.K., 2002; Aulton M.E., 2007; F.A.A. Adam. et. al., 2007; http://www.pharmainfo.net)

A matrix system consists of active and inactive ingredients, that are homogeneously dispersed and mixed in the dosage form. It is by far the most commonly used oral controlled release technology and the popularity of the matrix systems can be attributed to several factors which will be discussed in the later section. The release from matrix type formulations governed by Fick's first law of diffusion.

$$J = dQt/dt = - D\, dC/dx$$

J is flux, or rate of diffusion, while Q is the amount diffused per unit of time t, and D is diffusion coefficient.

1.6.1. Advantages of matrix system:

Unlike reservoir and osmotic systems, products based on matrix design can be manufactured using conventional processes and equipments. Secondly, development cost and time associated with the matrix system generally are viewed as variables, and no additional capital investment is required. Lastly, a matrix system is capable of accommodating both low and high drug loading and active ingredients with a wide range of physical and chemical properties.

1.6.2. Limitations of the matrix systems:

As with any technology, matrix systems come with certain limitations. First, matrix systems lack flexibility in adjusting to constantly changing dosage levels as required by clinical study outcome. When new dosage strength is deemed necessary, more often than not a new formulation and thus additional resources are expected. Furthermore, for some products that require unique release profiles (dual release or delayed plus extended release), more complex matrix-based technologies such as layered tablets are required.

1.6.3. Types of matrix systems:

The matrix system can be divided into two categories depending on the types of retarding agent or polymeric materials.

(a) Hydrophobic matrix system:

This is the only system where the use of polymer is not essential to provide controlled drug release, although insoluble polymers have been used. As the term suggests, the primary rate-controlling components of hydrophobic matrix are water insoluble in nature. These ingredients include waxes, fatty acids, and polymeric materials such as ethyl cellulose, methyl cellulose and acrylate copolymer. To modulate drug release, it may be necessary to incorporate soluble ingredients such as lactose into formulation. The presence of insoluble ingredient in the formulations helps to maintain the physical dimension of hydrophobic matrix during drug release. As such, diffusion of active ingredient from the system is the release mechanism, and the corresponding release characteristic can be described by Higuchi equation known as square root of time release kinetic. The square root of time release profile is expected with a porous monolithic, where the release from such system is

proportional to the drug loading. In addition, hydrophobic matrix systems generally are not suitable for insoluble drug because the concentration gradient is too low to render adequate drug release. As such, depending on actual ingredient properties or formulation design, incomplete drug release within the gastrointestinal transit time is a potential risk and need to be delineated during the development. With the growing needs for optimization of therapy, matrix systems providing programmable rates of delivery become more important. Constant rate delivery always has been one of the primary targets of controlled release system especially for drug with narrow therapeutic index.

(b) Hydrophilic matrix system:

The primary rate limiting ingredients of hydrophilic matrix are polymers that would swell on contact with aqueous solution and form a gel layer on the surface of the system. When the release medium (i.e. water) is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process, due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly out of the matrix. On the other hand, it would take more time for drug to diffuse out of the matrix since the diffusion path is lengthened by matrix swelling. Moreover, it has been widely known that swelling and diffusion are not the only factors that determine the rate of drug. For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate. While either swelling or dissolution can be the predominant factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms. The

presence of water decreases the glassy-rubbery temperature (for HPMC from 184°C to below 37°C), giving rise to transformation of glassy polymer to rubbery phase (gel layer). The enhanced motility of the polymeric chain favours the transport of dissolved drug. Polymer relaxation phenomena determine the swelling or volume increase of the matrix. Depending on the polymer characteristics, the polymer amount in the rubbery phase, at the surface of the matrix, could reach the disentanglement concentration; the gel layer varies in thickness and the matrix dissolves or erodes. The concentration at which polymeric chains can be considered disentangled was demonstrated to correspond to an abrupt change in the rheological properties of the gel. This showed a relationship between rheological behaviour of HPMC gels and their erosion rate, conforming that the polymer-polymer and polymer-water interaction are responsible for the gel network structure and its sensitivity to erosion. In turn, they affect drug release rate in the case of poorly soluble drugs. Swelling controlled release systems are based upon these principles. Due to the viscoelastic properties of the polymer which are enhanced by the presence of cross-linked network, anomalous penetrant transport can be observed. This behaviour is bound by pure Fickian diffusion and case II transport. Therefore, transport can be reduced to three driving forces. The penetrant concentration gradient, polymer concentration gradient and osmotic force behavior are observed as a result of polymer network. Appropriate polymer can counterbalance normal Fickian diffusion by hindering the release of embedded drug, leading to an extended period of drug delivery, and possibly zero-order release.

Drug release from swellable matrix tablets can be affected by glassy-rubbery transition of polymer (as a result of water penetration into the matrix where

interaction among water, polymer and drug or fillers is considered as the primary factor for release control) and the various formulation variables, such as polymer grade and type, drug to polymer ratios, drug solubility, drug and polymer particle sizes, compaction pressure and presence of additives or excipients in the final formulation. They concluded that, the release rate and mechanism of atenolol releases from hydrophobic and hydrophilic matrices are mainly controlled by the drug to polymer ratio. The results also showed that an increase in the concentration of fillers resulted in an increase in the release rate of the drug from matrices and hydrophilicity or hydrophobicity of the fillers had no significant effect on the release profile. Regarding the mechanism of release, the results showed that in most cases the drug release was controlled by both diffusion and erosion depending on the polymer type and concentration. On the other hand, incorporation of water soluble fillers like polyethylene glycol, lactose and surfactant into gel forming matrices can improve phenomenon of insufficient drug release, because these excipients can enhance the penetration of the solvent or water into the inner part of matrices, resulting in drug release from the matrices.

(c) Lipid matrix system:

These materials manufactured by the lipoid waxes and related ingredients. Active form of drug from the dosage form release the content such a matrices followed by either diffusion or erosion. A drug release properties are mainly depends on the absorption medium fluid component than hydrophobic polymers. Either Stearyl alcohol or stearic acid mixed with carnauba wax it has been mainly applicable for release retarding polymer in sustained release formulation of tablet.

(d) Biodegradable matrix system:

These types of polymer are biodegraded either by enzymatic or non enzymatic process. It contains the polymeric substance which is composed of monomeric linking to other functional group and gives unstable linkage in the backbone. Consist of the polymers which comprised of monomers linked to one another functional groups and have unstable linkage in the backbone. Finally the biodegraded material is excreted in the enzymatic process. Examples of naturally obtaining type polymers such as protein and polysaccharides; modified synthesized process of natural polymers; synthetic polymers like aliphatic poly ester and poly anhydride.

1.6.4. Polymers used in hydrophilic matrices: *(F.A.A. Adam, et. al., 2007)*

Hydrogel polymers were much investigated in literature on basis of drug release and release mechanism from hydrophilic matrix tablets as well as pellets. HPMC polymers achieve considerable attention due to their unique properties, and they can display good compression characteristics, including when directly compressed. They are nontoxic and can accommodate high level of drug loading, and also having adequate swelling properties that allows rapid formation of an external gel layer which retards or plays a major role in controlling drug release.

Furthermore, HPMC polymers are well known as pH-independent materials, this advantage enable them to withstand fluctuations of pH induce by intra and intersubject variations of both gastric pH and gastrointestinal transit time. They have been used alone or in combination in formulation of matrix tablets, therefore the hydrophilic gel forming matrix tablets are extensively used for oral extended release dosage forms due to their simplicity, cost effectiveness and reduction of the risk of

systemic toxicity which happens as a result of dose dumping. The release of diclofenac sodium from a mixture of HPMC, Carbopol 940, and lactose as water soluble fillers. The results showed that the combination of hydrogels retarded the drug better than single polymer. The principal advantage of HPMC matrix formulations is the drug release rates are generally independent of processing variables such as compaction pressure, drug particle size, increasing of initial granulation liquid and incorporation of lubricants.

The relationship between particle size, tensile strength and the viscosity grade of HPMC was complicated. At smaller particle size, an increase in the viscosity grade of HPMC resulted in a reduction in the tensile strength of its compacts. However, at the large particle size, the tensile strength of HPMC compacts decreased with an increase in viscosity grade. For HPMC K100M, there was an increase in tensile strength. The combination of HPMC and HPC at different ratios was investigated. Increasing the HPMC-HPC ratio increased both the particle size of granules and the tablet hardness. The drug release of HPMC matrix tablets was slightly influenced by type and concentration of diluents, but the viscosity grade of the polymer did not affect the release mechanism.

An increase in crushing strength of tablets made of Macrogol 6000 and HPMC, due to an increase in compression force during tableting stage and the dissolution of formulated tablet was significantly affected by increasing HPMC concentration.

Once daily propranolol extended release tablets using HPMC polymer as a retarding agent. The mechanism of the drug release from HPMC matrix tablet

followed non-Fickian diffusion, while the in vivo absorption and in vitro dissolution showed a linear relationship.

Other polymers used in hydrophilic matrix preparations include poly ethylene oxide, hydroxypropyl cellulose and hydroxyl ethyl cellulose.

Xanthan gum (XG) was widely used as a thickening agent in food industries, but recently introduced in pharmaceutical formulations It is a high molecular weight extracellular heteropolysaccharide, produced by fermentation with the gram-negative bacterium *Xanthamonas campestris.* XG shows excellent swelling properties and the swelling of the XG polymer matrix shows a square root of time dependence whereas drug release is almost time independent.

Carbopol is a derivative of polyacrylic acid. It is a synthetic, high molecular weight, crosslinked polymer. It is readily hydrates, absorbs water and swell. In addition, its hydrophilic nature and highly crossliked make it a potential candidate and has been used in controlled release drug delivery systems. In the case of tablets formulated with Carbopol polymer, the drug is entrapped in the glassy rubbery core in the dry state. It forms a gelatinous layer upon hydration. However, this gelatinous layer is significantly different structurally from the traditional matrix tablets. The hydrogel is not entangled chains of polymer, but discrete microgel made up of many polymer particles in which the drug is dispersed. The crosslinked network enables the entrapment of drug in the hydrogel domains. Since these hydrogels are not water soluble they do not dissolve, and erosion in the manner of linear polymer does not occur. Rather, when the hydrogel is fully hydrated, osmotic pressure from within works to break up the structure, essentially by sloughing off discrete pieces of the

hydrogel. This hydrogel remains intact, and the drug continues to diffuse through the gel layer at a uniform rate.

It is well recognized that key formulation variables are matrix dimension and shape, polymer level and molecular weight, as well as drug loading and solubility. Other factors such as tablet hardness, type of inactive ingredients and processing normally play secondary roles. The choice of manufacturing process such as direct blending or granulation typically does not affect product performance significantly, although exception does exist. In general, processing and scale-up associating with hydrophilic matrices are more robust than other controlled release systems.

1.6.5. Drug release from matrix systems: *(http://www.pharmainfo.net)*

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. Derivation of the mathematical model to describe this system involves the following assumptions:

a) A pseudo-steady state is maintained during drug release,

b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix,

c) The bathing solution provides sink conditions at all times.

The release behavior for the system can be mathematically described by the following equation,

$$dM/dh = Co.dh - Cs/2 \ldots\ldots\ldots\ldots 1$$

Where,

dM = Change in the amount of drug released per unit area

dh = Change in the thickness of the zone of matrix that has been depleted of drug

Co = Total amount of drug in a unit volume of matrix

Cs = Saturated concentration of the drug within the matrix.

Additionally, according to diffusion theory,

$$dM = (Dm.Cs)/h \, . \, dt \text{.....2}$$

dM = Change in the amount of drug released per unit area

dh = Change in the thickness of the zone of matrix that has been depleted of drug

Co = Total amount of drug in a unit volume of matrix

Cs = Saturated concentration of the drug within the matrix.

By combining equation 1 and 2 and integrating

$$M = [Cs \, . \, Dm \, . \, (2 \, Co - Cs \, . \, t \,)]1/2 \ldots\ldots 3$$

When the amount of drug is in excess of the saturation concentration, then

$$M = [Cs \, . \, Dm \, . \, Co \, . \, t]^{1/2} \, . \ldots\ldots\ldots\ldots 4$$

Equation 3 and 4 indicates the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix,

$$M = [2 \, D. \, Ca \, . \, p \, / \, T. \, (2 \, C_O - p. \, Ca \,) \, t]^{1/2} \ldots\ldots 5$$

Where, p = Porosity of the matrix

t = Tortuosity

Ca = solubility of the drug in the release medium

Ds = Diffusion coefficient in the release medium

T = Diffusional pathlength

For pseudo steady state, the equation can be written as,

$$M = [2\ D\ .\ Ca\ .\ CO\ (\ p\ /\ T\ )\ t]^{1/2} \text{…….6}$$

The total porosity of the matrix can be calculated with the following equation,

$$p = pa + Ca\ /\ \rho + Cex\ /\ \rho ex\ \text{..……..}\ 7$$

Where,

p = Porosity

ρ = Drug density

pa = Porosity due to air pockets in the matrix

ρex = Density of the water soluble excipients

Cex = Concentration of water soluble excipients

For the purpose of data treatment, Equation 7 can be reduced to,

$$M = k\ .\ t^{1/2}\ \text{..……..}\ 8$$

Where k is a constant, so that the amount of drug released versus the square root of time will be linear. If the release of drug from matrix is diffusion-controlled. In this case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters,

- Initial concentration of drug in the matrix
- Porosity
- Tortuosity

- Polymer system forming the matrix
- Solubility of the drug.

1.7. Methods used in tablet manufacturing: *(Lieberman H.A. and Lachman L., 1999; Ansel H.C., 2009)*

A. Wet granulation

B. Dry granulation

C. Direct compression

Granulation:

Generally the powders material cannot be punching directly into tablet form, because (a) the material should not have bonding a property to each other into compaction and (b) insufficient flow character from the hopper into die cavity. For this reason and this nature of material we can go for granulation methods.

The reason for granulation:

- Become the pharmaceutical ingredient are free flowing
- Increase the denseness of ingredient
- We can formulate uniform granular size that does not existing apart
- Produce better compression characteristic of drug
- Controlling the rate of drug release from the dosage form
- Reduce dust in granulation technique
- The appearance of tablet can be achieved

A. Wet granulation:

Size reduction of active ingredient and inactive ingredient, proper mixing of crushed powders, preparation of binder solution by using standard binder, pouring the binding agent with powder mixture to form coherent mass, the wet mass is screening

using 6 to 12 sieve mesh, drying the shifted granules, sieving prepared granules with lubricant and glidant, mixing screened granules with lubricant and glidant, finally compressed into tablet form.

Advantages:

- Powder material is converted into granular form by adding binding solution, the use of binder it's coating the each powder material to get a granules which having better cohesiveness and compressibility for manufacturing of tablet.
- If an active component it has been high label claim and also improper flow characteristic can be prepared by wet granulation technique to acquire excellent flow of granules and its granular material having cohesiveness for punching.
- Uniform distribution of active ingredient as well as uniform active content quantity of prepared dosage form.
- In many pharmaceutical ingredient can cause the dust and airborne pollute it could be handling without producing this problem by granulation method.
- In these methods prevent the agglomeration of ingredient in a homogeneous powder mixture under processing, shifting and handling.
- Controlled release dosage form can be developed by the manufacturing scientist using better binding agent and polymer or solvent.
- This procedure entrapment of air in the material can be reduced.

Disadvantages:

- It needs a number of equipments in the production area.
- There is a chances of pollute than the direct compression method.
- In these method timing period is increase because moistening the material and drying process.

- This method not suitable for sticky ingredient and hygroscopic substance.

B. Dry granulation:

In dry granulation size reduction of active ingredient and inactive ingredient, mixing of milled material, directly compressed into tablet, further the prepared tablet is milled this process called slugging, sieving of slug material, finally mixing with lubricant and glidant and tablet punching.

Advantages:

- In this method the material are highly heats sensitive and destroyed in moisture condition so we can formulate by dry granulation method.
- It needs less space for placing the equipment and processing step than other methods.
- The ingredient cost is smaller in extent.

Disadvantages:

- For this method, either the active material or inactive material should have binding properties and cohesive nature.
- The ingredient must be in the nature of either crystalline or amorphous form.

C. Direct compression:

Size reduction of active component and inactive component, mixing of milled ingredients, tablet compression.

Advantages:

- The exposing of active component to moisture and thermal can be prevented.
- These methods the cost of preparation can be minimized and reduce the labor cost.

❖ Tablet manufactured by this process very easy to disintegrating molecule from the dosage form.

❖ The equipment like granulators and dryers and solvent are not needed in manufacturing of tablets by this method.

Disadvantages:

❖ The uniformity of color is difficult to achieve in manufacturing of tablets.

❖ In this process cost of materials is a great vertical extent.

❖ In this method produce dust and air pollute during manufacturing process.

❖ Content uniformity is not maintained, because agglomeration and separation of drug molecule it will occur in transferring from hopper into die cavity.

1.8. ARTHRITIS: *(Tripathi K.D., 2003; Rang A.P., et al., 2001; Brunton L., et al., 2008)*

"Arthritis" literally means "inflamed joints". Arthritis primarily affects the joints; it also attacks muscles and connective tissues of the surrounding organs. Arthritic disease stems from injuries, defects in the immune system, wear and tear on the joints, infections or genetic predisposition.

A. Osteoarthritis:

A degenerative joint disease and the most common form of arthritis and joint disorders, is the gradual deterioration of cartilage, usually in the larger, weight bearing joints such as the hips, knees, and spine. This wear and tear is normal process predominantly found in people of age 55 and older. Among those younger than 45, it occurs more often in men. The joints are not always inflamed; the articular cartilage may begin to flake and crack, due to over use or injury. In severe cases the underlying bone becomes thickened and distorted. Scar tissue may then

replace damaged cartilage. If movement becomes painful and restricted, lessened use of the associated muscles will lead to their atrophy.

B. Rheumatoid arthritis:

Rheumatoid arthritis is traditionally considered a chronic, inflammatory autoimmune disorder that causes the immune system to attack the joints. It is a disabling and painful inflammatory condition, which can lead to substantial loss of mobility due to pain and joint destruction. Rheumatoid arthritis is a systemic disease, often affecting extra articular tissues throughout the body including the skin, blood vessels, heart, lungs and muscles.

The joint lining, called the synovium, becomes inflamed in cases of rheumatoid arthritis, leading to pain, stiffness, warmth, redness and swelling. These inflamed cells release an enzyme that may even digest cartilage and bone.

1.8.1 Biochemical mechanism:

The normal synovial lining of diarthodial joints is a delicate tissue layer up to three cells thick and a loosely arranged stroma with connective tissue, microvasculature and lymphatics. Inflammatory synovitis is the key pathological feature in rheumatoid arthritis. Its characteristics are synovial hyperplasia, inflammatory cell infiltration and vascularity. Initially edema and fibrin deposition predominate. Subsequently, there is synovial lining layer hyperplasia involving macrophage and fibroblast like synoviocytes. This hyperplasia is accompanied by infiltration of T cells, B cells, macrophages and plasma cells in the sublining layer.

A number of different pathological mechanisms are involved in rheumatoid arthritis. Lymphocytes have an important role and many inflammatory cells in the synovial sublining layer are lymphocytes, especially T cells.

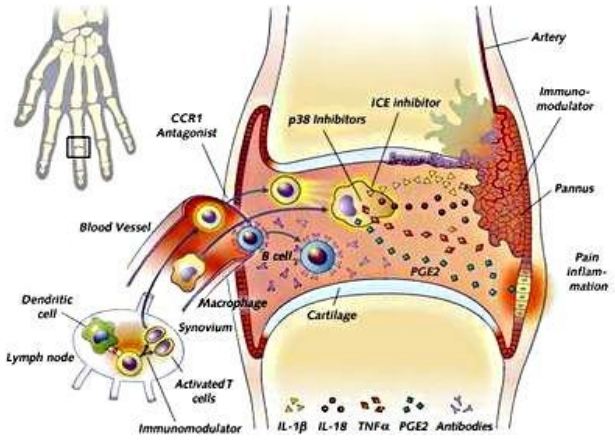


Figure 1.8: The Pathophysiology of Rheumatoid Arthritis

1.8.2. Symptoms:

The exacerbation of the disease peaks at only certain times of the day and the cardinal symptoms of rheumatoid arthritis include:

- Stiffness, swelling and pain of one or more joints of the body characteristically severe in the morning, fatigue and weakness.
- Stiffness following periods of immobility, which gradually improves with movement.
- Rheumatoid nodules (lumps of inflamed cells) under the skin usually found on the bony part of the fore arm, ankle and fingers.
- Minor fever, anemia and weight loss.

1.8.3. Treatment:

Pharmacological treatment of rheumatoid arthritis can be divided into

- Disease modifying anti-rheumatic drugs
- Anti-inflammatory agents and analgesics.

- DMARDs have been found to produce durable remissions and delay or halt disease progression. In particular they prevent bone and joint damage from occurring secondary to the uncontrolled inflammation.

1.8.4. Disease modifying anti-rheumatic drugs (DMARDs):

DMARDs can be further subdivided into Xenobiotic agents and biological agents. Xenobiotic agents are those DMARDs that do not occur naturally in the body, as opposed to biologicals.

Xenobiotics include,

Azathioprine, Cyclosporine, D-penicillamine, gold salts, Leflunomide, Minocycline, Hydroxychloroquine, Methotrexate, and Sulfasalazine.

Biological agents:

Tumor necrosis factor (tnf α) blockers - Etanercept (Enbrel), Infliximab (Remicade),

Interleukin-1 blockers - Anakinra

Anti-B cell (CD20) antibody - Rituximab

1.8.5. Anti-inflammatory agents and analgesics:

The treatment of arthritic conditions relies on medicines that fight joint swelling, stiffness and pain. Circadian rhythm affects the arthritic medication. NSAIDs reduce the swelling, stiffness and pain of arthritis. Taking the medicines at the wrong time of day compromises their effectiveness and increases the risk of side effects such as indigestion, stomach ulcers, headache, anxiety and dizziness. Chronotherapy provides ways of increasing the effectiveness and safety of arthritic medications.

Anti-inflammatory agents include,

A. Glucocorticoids:

Non steroidal anti-inflammatory drugs also act as analgesics.

B. Non steroidal anti -inflammatory drugs:

NSAIDs are drugs with analgesic, antipyretic and anti inflammatory effects that reduce pain, fever and inflammation. The term "non steroidal" is used to distinguish these drugs from steroids, which (among a broad range of other effects) have a similar eiconoside depressing, anti inflammatory action.

Mechanism of action:

Most NSAIDs act as non selective inhibitors of the enzyme cyclooxygenase, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes.

Cyclooxygenase catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (Derived from the cellular phospholipid bilayer by phospholipase A2).

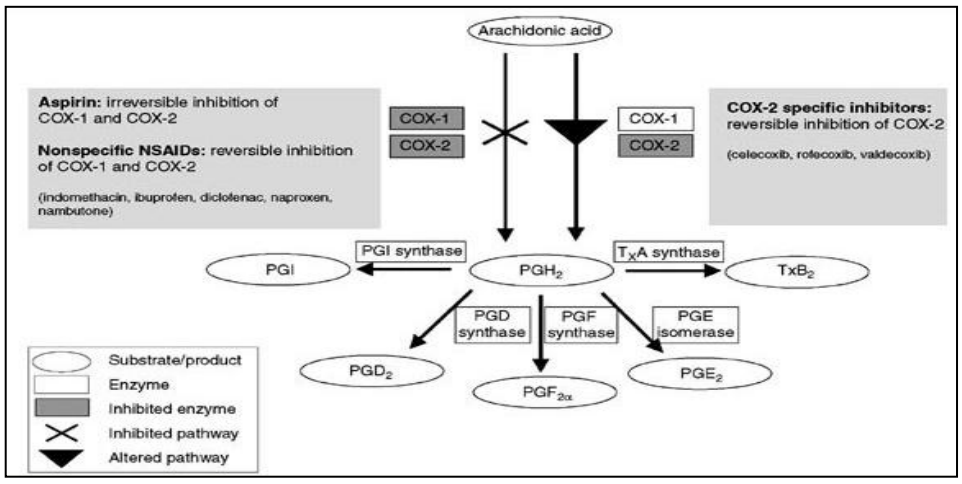


Figure 1.9: Mechanism of action of NSAIDs

1.8.6. Classification of NSAIDs:

A. Chemical classification:

Table 1.1: Classification of NSAIDs

S.No.	Category	Drug
1.	Salicylates	Aspirin
2.	Indoles	Indomethacin
3.	Pyrazoles	Phenyl butazone
4.	Fenamate	Mefenamic acid
5.	Propionic acid	Ibuprofen, Ketoprofen
6.	Phenyl acetic acid	Diclofenac, Aceclofenac, Flurbiprofen
7.	Oxicam	Piroxicam, Tenoxicam, Meloxicam
8.	Sulphonanilide	Nimesulide
9.	Coxibs	Celecoxib, Rofecoxib,Valdecoxib, Parecoxib
10	Alkanone	Nabumetone
11	Aryl propionic acid	Naproxen

B. Classification based on COX selectivity:

1. **Non COX selective NSAIDS:**

   Aspirin, Indomethacin, Diclofenac, Piroxicam, Ibuprofen, Naproxen, Mefenamic acid.

2. **Preferential COX-2 inhibitors:**

   Nimesulide, Meloxicam, Nabumetone, Aceclofenac

3. **Highly selective COX-2 inhibitors:**

   1st generation **:** Celecoxib, Rofecoxib

   2nd generation **:** Valdecoxib, Parecoxib, Etoricoxib, Lumiracoxib.

Need & Objective

2. NEED AND OBJECTIVE

Aceclofenac is a non-steroidal anti-inflammatory, analgesic and antipyretic agent. It is a prodrug of Diclofenac, in the inflammatory cells it gets converted into diclofenac and 4-hydroxy diclofenac. Aceclofenac has the more COX-2 specificity than diclofenac, as it is active only in inflammatory cells it has less GI stress than diclofenac. It has short biological half-life (4 hours), and the usual oral dosage regimen is 100 mg taken 2 times a day.

The basic goal of therapy is to achieve a steady state blood or tissue level that is therapeutically effective and non-toxic for an extended period of time. Sustained release drug delivery systems, with an aim of improved patient compliance, better therapeutic efficacy, less side effects and reduced dosage regimen with less toxicity for treatment for many acute and chronic diseases.

Non–Steroidal Anti-Inflammatory Drugs (NSAIDs) are considered to be the first line drug in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Aceclofenac is one of the emerging NSAIDs molecules for arthritis treatment

- To minimize the frequent dosing
- To prolong the pharmacological effect and
- To improve patient compliance, a sustained release formulation of Aceclofenac is very much desirable.

Among the many techniques used for modulating the drug release profile, the most commonly used method is embedment of the drug into a polymer matrix.

The matrix may be formed by either dissolving or dispersing the drug uniformly in the polymer mass. Such polymer matrices can give,

- Desirable release profiles
- Cost effective manufacturing method and also
- Broad regulatory acceptance.

Hence, in the present work, an attempt is made to develop sustained-release matrix tablets of Aceclofenac, with the use of various hydrophilic polymers for their sustaining effect. Wet granulation technique is used for tablet formulation along with the addition of suitable additives by using of hydrophilic polymers of HPMC K15M, Carboxy methyl cellulose and Xanthan gum.

Objectives of the work:

To design of sustained release dosage form of Aceclofenac that will help in releasing only small quantities of drug over a prolonged period of time.

- To study the effect of type of polymers and polymer concentration on release profiles of sustained release Aceclofenac formulations.
- To study the different types of schemes on release profiles of sustained release Aceclofenac formulations.
- To arrive at better formulation based on comparison amongst the studied ones.
- To perform stability studies as per ICH guidelines.

Plan of Work

3. PLAN OF WORK

- **Literature survey**
- **Selection and procurement of suitable drug candidate and excipients**
- **Preformulation studies**
  - **Characterization of drug**
    - Melting point determination
    - Solubility determination
    - UV spectra (λ_{max})
    - IR spectra
    - Loss on drying
    - Standard carve of Aceclofenac
    - Percentage purity of drug
  - **Drug polymer interaction study**
    - Fourier transform Infra-Red (FTIR) spectroscopy
    - Differential Scanning Calorimetry (DSC**)**
  - **Characterization of Powdered blend**
    - Bulk density
    - Tapped density
    - Carr's index
    - Hausner's ratio
    - Angle of repose

- **Formulation of Sustained release matrix tablet of Aceclofenac**
- **Evaluation of Sustained release matrix tablet of Aceclofenac**
    - Appearance
    - Dimensions (Thickness and Diameter)
    - Hardness
    - Percent friability
    - Weight variation test
    - Drug content of Aceclofenac (assay)
    - In-vitro dissolution studies
    - Kinetic of *In-vitro* Drug Release
- **Stability studies**
- **Result and discussion**
- **Summary and conclusion**

Literature Review

4. LITERATURE REVIEW

Sahoo S.K., *et al.*, (2008): In the present study Aceclofenac gelatin micropellets were prepared by cross linking technique using glutaraldehyde has a cross linking agent. The effect of the drug polymer ratio, temperature of oil phase amount of glutarldehyde and stirring micropellets having an entrapment efficacy, micropellets size and drug release characteristics spherical micropellets having an entrapment efficiency of 57-97% were obtained.

Keny R.V., *et al.*, (2009): The present study was aimed to develop once daily extended release matrix tablets of minocycline hydrochloride, using hydroxyl propyl methyl cellulose either alone or in combination with ethyl cellulose as the matrix material in different proportions. The formulated tablets were also compared with a marketed product. The results of the dissolution study indicate that formulations FC-IV, FC-V, FC-VI, shows maximum drug release upto 24 hr. Drug release from matrix occurred by combination of two mechanisms diffusion of tablet matrix and erosion of tablet surface which was reflected from Higuchi's model and Erosion plot.

Nasra M.A., *et al.*, (2007): The potential of matrix, multilayer and compression coated tablets of metronidazole to reach the colon intact has been investigated *in vitro*, using pectin as a carrier. Matrix tablets containing various proportions of pectin were prepared by wet granulation and direct compression techniques. *In vitro* release studies indicated that matrix and multilayer tablets failed to control the drug release in the physiological environment of stomach and small intestine, compression coated tablet formulations F13, F14 and F12 released about

70.25% ± 9.9%, 51.3% ± 5.45% and 20% ± 5.01% drug respectively at the end of 24 hours. These tablets exhibited no change either in physical appearance or dissolution pattern after storage at ambient temperature (25°C) for 12 months.

Manjanna K.M., *et al.*, (2009): The objective of the present study was microencapsulate the Aceclofenac (NSAIDs) by ionotropic gelation technique by using sodium alginate as hydrophilic carrier in various polymer interactions were observed in FT-IR studies. *In-vitro* drug release profile of Aceclofenac from microbeads was examined in simulated gastric fluid pH1.2 for initial 2 h, mixed phosphate buffer pH6.8 upto 6 h and simulated intestinal pH 7.2 at end of 24 h studies. The release of drug from the microbeads was pH dependent, showed negligible drug release in pH1.2. Under neutral conditions the beads will swell and the drug release depend on the swelling and erosion process resulting optimum level of drug released in a sustained manner and exhibited zero-order kinetics followed by super case-II transport.

Ganesan V., *et al.*, (2008): The objective of the study was to develop guar gum matrix tablets for oral controlled release of Ambroxol hydrochloride. According to the theoretical release profile calculation, a twice daily sustained release formulation should release 19.6 mg of Ambroxol hydrochloride in 1 hour like conventional tablets, and 5.2 mg per hour upto 12 hours. Ambroxol hydrochloride matrix tablets containing either 30%wt/wt of low viscosity (F-III), 25% wt/wt medium viscosity (F-VI) or 20% wt/wt high viscosity (F-IX) guar gum showed sustained release. Applying exponential equation, the selected formulations F-III and

F-VI showed diffusion-dominated drug release and followed first order kinetics. The mechanism of drug release from F-IX was diffusion coupled with erosion.

Gothi G.D., *et al.*, (2010): In the present investigation an attempt was made to reduce the frequency of dose administration, to prevent nocturnal heart attack and to improve the patient compliance by developing extended release (ER) matrix tablet of metoprolol succinate. The effect of concentration of hydrophilic (HPMC K100M, Xanthan gum) on the release rate of metoprolol succinate was studied.

Anton S.A., *et al.*, (2009): The objective of the present work was to develop sustained release matrix tablets of Ondansetron Hydrochloride (5mg) formulated employing Hydroxy propyl Methyl Cellulose (HPMC), polymer and the sustained release behavior of the tablets was investigated. Tablets were prepared by wet granulation methods.

Krishnaiah Y.S.R., *et al.*, (2004): The objective of the present study is to carry out pharmacokinetic evaluation of oral controlled release formulation (guar gum-based three layer matrix tablets) containing highly soluble metoprolol tartrate as a model drug. The plasma concentration of metoprolol tartrate was estimated by reverse-phase HPLC. The pharmacokinetic parameters were calculated from the plasma concentration of metoprolol tartrate versus time data. The results of the study indicated that guar gum three-layer matrix tablets were able to provide oral controlled delivery of highly water-soluble drug such as metoprolol tartrate in humans.

Mishra B., *et al.*, (2005): The present study aimed to formulate and evaluate hydrophilic matrix tablets of diltiazem hydrochloride to achieve a controlled and sustained drug release with reduced frequency of drug administration, reduced side

effects and improved patient compliance. Matrix tablets of diltiazem hydrochloride were prepared using polymers like hyroxypropyl methylcellulose (HPMC K15M, HPMC K4M), sodium carboxy methylcellulose (SCMC) and Guar gum, and different diluents like lactose, starch, microcrystalline cellulose.

Chandria M., *et al.*, (2009): The present investigation attempt has been made increase therapeutic efficacy, reduce frequency of administration and improve patient Compliance, by developing sustained release matrix tablets of Zidovudine, were developed by using drug polymer ratio of kollidon SR, HPMC K15M and HPMC K100M as matrix tablet formulation were compressed by direct compression and wet granulation method. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, thinkess, *in-vitro* dissolution, and swelling index, all formulation showed compliance with pharmacopoeial standards.

Morkhade D.M., *et al.*, (2007): Natural gum, damer was investigated as a novel microencapsulating material for sustained drug delivery. Microparticles were prepared by oil-in-oil emulsion solvent evaporation method. Ibuprofen and diltiazem hydrochloride were used as model drugs. *in-vitro* drug release kinetics.. The increase in gum:drug ratio showed an increase in particle size, encapsulation efficiency and decrease in drug release rate in all cases. Drug release profiles of all microparticles followed zero order kinetics.

Saptarshi D., *et al.*, (2010): An attempted was to formulate the oral sustained release metformin hydrochloride matrix tablets by using hydroxyl methyl cellulose polymer (HPMC) as rate controlling factor and to evaluate drug release parameters as per various release kinetic models. It is observed that the basic goal of therapy in the

development of metformin hydrochloride release dosage form is to increase bioavailability; reduce risk of hospitalization, deliver drug at a near constant rate for approximately 12h; independent of food intact and gastrointestinal pH. The dry granulation technique was used to compress the tablet as powder showed the poor flowability; wet granulation technique was not selected for the present work.

Sarojini S., *et al., (*2010): The purpose investigation highlights the formulation and optimization of floating tablets of Theophylline as a model drug. Formulations were optimized for type of filler and different concentration of Polyethylene oxide.

Tabandeh H., *et al.,* (2003): A sustained release tablet formulation should ideally have a proper release profile insensitive to moderate changes in tablet hardness that is usually encountered in manufacturing. In the study, matrix Aspirin (acetylsalicylic acid) tablets with ethyl cellulose (EC), Eudragit RL100, Eudragit S100 were prepared by direct compression. The release behaviors were then studied in two counterpart series of tablets with hardness difference of three Kp units, and compared by non-linear regression analysis.

Varshosaz J., *et al.,* (2002): The buccoadhesive controlled-release tablets for delivery of Nifedipine were prepared by direct compression of carboxymethyl cellulose (CMC) with carbomer (CP), which showed superior bioadhesion properties compared to polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), hydroxypropyl methylcellulose (HPMC), and acacia in a modified tensiometry method in vitro. The tablets containing 30 mg of Nifedipine and various amounts of CMC and CP showed a zero-order drug release kinetic.

Yeole P.G., *et al.,* (2006): In the present investigation, an attempt has been made to increase therapeutic efficacy, reduce frequency of administration, and improve patient compliance, by developing sustained release matrix tablets of Diclofenac sodium. Sustained release matrix tablets of Diclofenac sodium, were developed by using different drug:polymer ratios, such as F1(1:0:12), F2(1:0:16), F3(1:0:20), F4(1:0:24) and F5(1:0:28). Xanthan gum was used as matrix former, and microcrystalline cellulose as diluents. All the lubricated formulations were compressed using 8mm flat faced punches.

Ghosh S., *et al.,* (2009): The objective of the study was to develop matrix tablets for oral controlled release of Aceclofenac. Matrix tablets of Aceclofenac, using various viscosity of hydrophilic polymer HPMC in two different proportions, hydrophobic polymer ethyl cellulose and Guar gum were prepared by wet granulation method and subjected to *in vitro* drug release studies. The drug release from all HPMC matrix tablets followed various release kinetics, formulation no - F7 followed Higuchi kinetics. Furthermore, the results of the *in vitro* studies in pH 7.5 phosphate buffer medium showed that F7 tablets provided controlled release comparable with market sustained release formulation (Aeroff-SR tablets).

Radika P.R., *et al.,* (2008): Delayed release microspheres of Aceclofenac were formulated using enteric polymer, Cellulose acetate phthalate (CAP) prepared by solvent evaporation technique. The effect of various other modern enteric polymers such as HPMC, Eudragit L-100, Eudragit S-100 on the release of Aceclofenac from the CAP have been evaluated.

Soni T., *et al.*, (2008): The development of a meaningful dissolution procedure for drug products with limited water solubility has been a challenge to the pharmaceutical industry. Aceclofenac (BCS Class II drug) is a non steroidal anti-inflammatory drug. There is no official dissolution medium available in the literature. In the present study, parameters such as solubility, medium pH, surfactant type, dissolution behavior of formulations, and influence of sink conditions, stability, and discriminatory effect of dissolution testing were studied for the selection of a proper dissolution medium.

Srinivas Mutalik., *et al.*, (2008): The purpose of this study was to develop a once daily sustained release tablet of Aceclofenac using chitosan and an enteric coating polymer. Overall sustained release for 24 h was achieved by preparing a double-layer tablet in which the immediate release layer was formulated for a prompt release of the drug and the sustained release layer was designed to achieve a prolonged release of drug. Good equivalence in the drug release profile was observed when drug release pattern of the tablet containing chitosan and hydroxypropyl methylcellulose phthalate (M-7) was compared with that of marketed tablet.

Umesh.D. Shivhare., *et al.*, (2009): The objective of the present study was to develop "once daily" sustained release tablets of aceclofenac by wet granulation using carboxy -polymethylene polymer. The drug excipient mixtures were subjected to preformulation studies while the tablets were subjected to physicochemical studies, in vitro drug release, stability studies and validation studies.

Basak S.C., *et al.*, (2010): Monolithic matrix tablets of Ambroxol Hydrochloride were formulated as sustained release tablets employing Hydroxy

Propyl Methyl Cellulose polymer, and the sustained release matrix tablets containing 75mg Ambroxol hydrochloride were developed using different drug polymer ratios of Hydroxy Propyl Methyl Cellulose. Tablets were prepared by direct compression. Formulation was optimized on the basis of acceptable tablet properties and in vitro drug release.

Yadav I.K. *et al.,* (2010): The objective of the present study was to develop the oral sustained release matrix tablets of Aceclofenac using hydrophilic and hydrophobic polymers. Aceclofenac is a non steroidal anti-inflammatory agent used in symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis and its biological half life is 4 hrs. Controlled release formulations of Aceclofenac (200 mg) were prepared by direct compression method. The drug release from optimized formulations F1, F4 and F7 was extended for a period of 12 h. The kinetic treatment to optimized formulations showed that the release of drug follows zero order model and Super Case II transport for F1 and F7.

Suvakanta D., *et al.,* (2010): In this paper were reviewed mathematical models used to determine the kinetic of drug release from drug delivery system the quantitative analysis of the values are obtained in dissolution/ release rate is easier when mathematical formula used to describe the process. The mathematical modeling can optimize to design therapeutic design of therapeutic device to yield information on the various efficacy of various release models.

Kabir A.K., *et al.,* (2009): Objective of this study was to develop a sustained release matrix tablet of Aceclofenac using hydroxypropyl methylcellulose (HPMC K15M and HPMC K100M CR) in various proportions as release controlling factor by

direct compression method. The results of dissolution studies indicated that the formulations F-2 and F-3 could extend the drug release up to 24 hours. From this study, a decrease in release kinetics of the drug was observed when the polymer concentration was increased. Kinetic modeling of *in vitro* dissolution profiles revealed the drug release mechanism ranges from diffusion controlled or Fickian transport to anomalous type or non-Fickian transport, which was only dependent on the type and amount of polymer used. The drug release followed both diffusion and erosion mechanism in all cases.

Drug & Excipients Profile

5. DRUG AND EXCIPIENT PROFILE

5.1. DRUG PROFILE : *(IP, 2007; BP., 2009; Kabir, et al., 2009)*

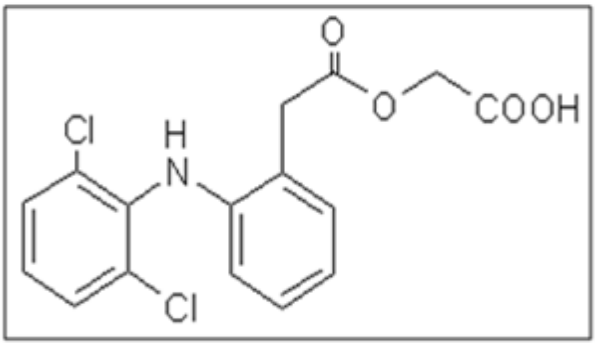
5.1.1. ACECLOFENAC:

Aceclofenac is a potent non-steroidal anti-inflammatory drug. Due to its preferential cox-2 blockage it has better safety than conventional NSAIDs with respect to adverse effects on gastro intestinal and cardiovascular system.

IUPAC Name **:** 2-[(2, 6-Dichlorophenylamino) phenyl] acetoxy acetic acid.

Description **:** A white to almost white crystalline powder.

Structure :



Molecular formula: $C_{16}H_{13}Cl_2NO_4$

Molecular weight: 354.2

Category **:** Non-steroidal anti inflammatory drug.

Solubility **:** It is practically insoluble in water; soluble in alcohol and methyl alcohol; It is freely soluble in acetone and dimethyl formamide.

Melting point **:** 149 - 150ºC

Pharmacology:

The mode of action of Aceclofenac is largely based on the inhibition of the prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme Cyclooxygenase, which is involved in the production of prostaglandins.

The drug inhibits synthesis of the inflammatory cytokines, interleukin (IL)-1 and tumor necrosis factor and prostaglandin (PGE_2) production. Effects on cell adhesion molecular from neurophils have also been noted. *In vivo* data indicate inhibition of Cyclooxygenase (COX-1 and 2) by Aceclofenac in whole blood says, with selectivity for COX-2 being evident.

Aceclofenac has shown stimulatory effects on cartilage matrix synthesis that may be linked to the ability of the drug to inhibit IL-1 activity. *In vitro* data indicate stimulation by the drug of synthesis of glycosaminoglycan in osteoarthritic cartilage. There is also evidence that Aceclofenac stimulates the synthesis of IL-1 receptor antagonist in human articular chondrocytes subjected to inflammatory stimuli and that 4'-hydroxyaceclofenac has chondroprotective properties attributable to Aceclofenac in patients with ankylosing spondylitis.

Pharmacokinetics:

Aceclofenac is rapidly and completely absorbed after oral administration, peak plasma concentration is reached 1 to 3 hours after an oral dose. The drug is highly protein bound. The presence of food does not alter the extent of absorption of Aceclofenac but the absorption rate is reduced. It is metabolized to a major metabolite 4-hydroxy aceclofenac and to a number of other metabolites including 5–hydroxy

aceclofenac, 4-hydroxy diclofenac. Renal excretion is the main route of elimination of Aceclofenac with 70 to 80 % of an administered dose found in the urine, mainly as the glucuronides of Aceclofenac and its metabolites of each dose of Aceclofenac, 20% is excreted in the faeces. The plasma elimination half life of the drug is approximately 4 hours.

Drug interactions:

Aceclofenac may increase plasma concentrations of lithium, digoxin and methotrexate, increase the activity of anticoagulant, inhibits the activity of diuretics, enhance cyclosporine nephrotoxicity and precipitate convulsions when co-administered with quinolone antibiotics. Furthermore, hypo or hyperglycemia may result from the concomitant administration of Aceclofenac and antidiabetic drugs, although this is rare. The co-administration of Aceclofenac with other NSAIDs results in increased frequency of adverse event.

Adverse drug interactions:

Aceclofenac is well tolerated with, most adverse events being minor and reversible and affecting mainly the G.I system. Most common events include dyspepsia (7.5%), abdominal pain (6.2%), nausea (1.5%), diarrohoea (1.5%), flatulance (0.8%), gastritis (0.6%), constipation (0.5%), vomiting (0.5%), and pancreatitis (0.1%). Other adverse effects which is not common such as dizziness (1%), vertigo (0.3%), and rare cases of paraesthesia and tremor.

Dosage and administration: The usual dose of Aceclofenac is 100 mg given twice daily by mouth, one tablet in the morning and one in the evening.

Storage: In an air tight container, protected from light.

Uses: Aceclofenac is used in the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, dental pain, post operative pain, dysmenorrhoea, acute lumbago, musculoskeletal trauma and gonalgia (knee pain).

5.2. Excipients profile:

5.2.1. HYPROMELLOSE: *(Raymond C. Rowe, 2003)*

1. Nonproprietary Names:

- **BP:** Hypromellose
- **JP:** Hydroxypropylmethylcellulose
- **PhEur:** Hypromellosum
- **USP:** Hypromellose

2. Synonyms:

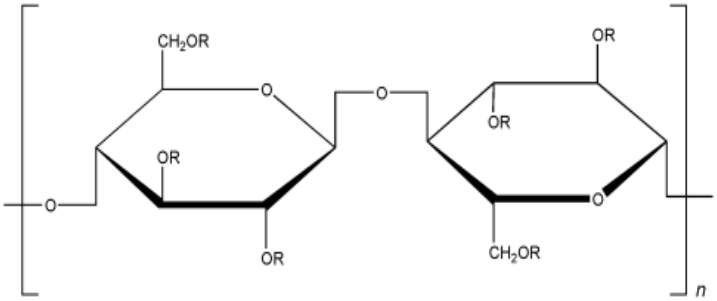
Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

3. Chemical Name and CAS Registry Number:

Cellulose hydroxypropyl methyl ether [9004-65-3]

4. Molecular Weight: 10,000–1,500,000.

5. Structural Formula:



Where R is H, CH_3, or CH_3CH (OH) CH_2

6. Functional Category: Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology:

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as matrix for use in extended-release tablet formulations. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2-20% w/w are used for film-forming solutions to film-coat tablets. Hypromellose at concentrations 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.

8. Description: Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

9. Typical Properties:

- **Acidity/alkalinity** **:** pH = 5.5–8.0 for a 1% w/w aqueous solution.
- **Density (bulk)** **:** 0.341 g/cm^3
- **Density (tapped)** **:** 0.557 g/cm^3
- **Density (true)** **:** 1.326 g/cm^3
- **Melting Point** **:** browns at 190–200°C; chars at 225–230°C

  Glass transition temperature is 170-180^{o}C

- **Solubility:** Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol.
- **Viscosity (dynamic):** A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w.

Table 5.1: Various Grades of Hypromellose

Methocel product	**USP 28 designation**	**Nominal viscosity (mPa s)**
Methocel K100 Premium LVEP	2208	100
Methocel K4M Premium	2208	4000
Methocel K15M Premium	2208	15 000
Methocel K100M Premium	2208	100 000
Methocel E4M Premium	2910	4000
Methocel F50 Premium	2906	50
Methocel E10M Premium CR	2906	10 000
Methocel E3 Premium LV	2906	3
Methocel E5 Premium LV	2906	5
Methocel E6 Premium LV	2906	6
Methocel E15 Premium LV	2906	15
Metolose 60SH	2910	50, 4000, 10 000
Metolose 65SH	2906	50, 400, 1500, 4000
Metolose 90SH	2208	100, 400, 4000, 15 000

10. Stability and Storage Conditions:

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively.

11. Incompatibilities:

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts.

5.2.2. CARBOXYMETHYLCELLULOSE SODIUM: *(Raymond C. Rowe, 2003)*

1. Nonproprietary Names:

- **BP:** Carmellose sodium
- **JP:** Carmellose sodium
- **PhEur**: Carmellosum natricum
- **USP:** Carboxymethylcellulose sodium

2. Synonyms:

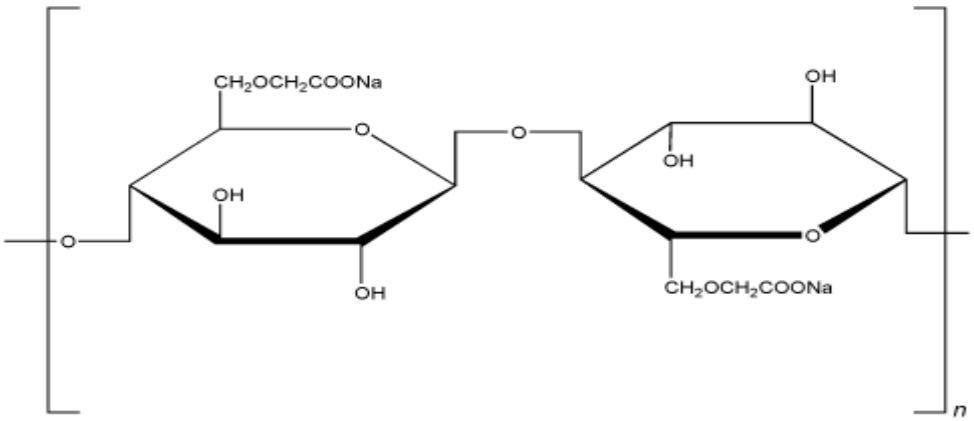
Cellulose gum; CMC sodium; SCMC; sodium carboxymethylcellulose; sodium cellulose glycolate; sodium CMC

3. Chemical Name and CAS Registry Number:

Cellulose, carboxymethyl ether, sodium salt [9004-32-4]

4. Molecular Weight: 90,000–7, 00,000

5. Structural Formula:



6. Functional Category:

Coating agent; stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent; water-absorbing agent.

7. Applications in Pharmaceutical Formulation or Technology:

Carboxymethylcellulose sodium is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity-increasing properties. Viscous aqueous solutions are used to suspend powders intended for either topical application or oral and parenteral administration. Carboxymethylcellulose sodium may also be used as a tablet binder and disintegrant and to stabilize emulsions.

Higher concentrations, usually 3–6%, of the medium-viscosity grade are used to produce gels that can be used as the base for applications and pastes; glycols are often included in such gels to prevent them drying out.

Carboxymethylcellulose sodium is additionally one of the main ingredients of self-adhesive ostomy, wound care and dermatological patches, where it is used as a mucoadhesive and to absorb wound exudate or transepidermal water and sweat. This muco-adhesive property is used in products designed to prevent post-surgical tissue adhesions; and to localize and modify the release kinetics of active ingredients applied to mucous membranes; and for bone repair. Encapsulation with carboxymethylcellulose sodium can affect drug protection and delivery. There have also been reports of its use as a cytoprotective agent. Carboxymethylcellulose sodium is also used in cosmetics, toiletries, surgical prosthetics, and incontinence, personal hygiene, and food products.

Uses	Concentration (%)
Emulsifying agent	0.25–1.0
Gel-forming agent	3.0–6.0
Injections	0.05–0.75
Oral solutions	0.1–1.0
Tablet binder	1.0–6.0

8. Description:

Carboxy methylcellulose sodium occurs as a white to almost white, odorless, granular powder.

9. Typical Properties:

- **Density (bulk)** **:** 0.52 g/cm^3
- **Density (tapped)** **:** 0.78 g/cm^3
- **Dissociation constant** **:** pKa=4.30
- **Melting Point** **:** browns at 227°C; chars at 252°C
- **Moisture Content:** Typically contains less than 10% water. However, carboxymethylcellulose sodium is hygroscopic and absorbs significant amounts of water at temperatures up to 37°C at relative humidities of about 80%.
- **Solubility**: Practically insoluble in acetone, ethanol (95%), ether, and toluene. Easily dispersed in water at all temperatures, forming clear, colloidal solutions. The aqueous solubility varies with the degree of substitution (DS).
- **Viscosity:** Various grades of carboxy methylcellulose sodium are commercially available that have differing aqueous viscosities. Aqueous 1% w/v solutions with viscosities of 5–13,000 mPa's (5–13,000 Cps) may be obtained. An

increase in concentration results in an increase in aqueous solution viscosity. Prolonged heating at high temperatures will depolymerize the gum and permanently decrease the viscosity. The viscosity of sodium carboxy methylcellulose solutions is fairly stable over a pH range of 4–10. The optimum pH range is neutral.

10. Stability and Storage Conditions:

Carboxy methylcellulose sodium is a stable, though hygroscopic material. Under high humidity conditions, carboxy methylcellulose sodium can absorb a large quantity (>50%) of water.

Aqueous solutions are stable at pH 2–10; precipitation can occur below pH 2, and solution viscosity decreases rapidly above pH 10. Generally, solutions exhibit maximum viscosity and stability at pH 7–9. Carboxy methylcellulose sodium may be sterilized in the dry state by maintaining it at a temperature of 160°C for 1 hour. However, this process results in a significant decrease in viscosity and some deterioration in the properties of solutions prepared from the sterilized material.

Aqueous solutions may similarly be sterilized by heating, although this also results in some reduction in viscosity. After autoclaving, viscosity is reduced by about 25%, but this reduction is less marked than for solutions prepared from material sterilized in the dry state. The extent of the reduction is dependent on the molecular weight and degree of substitution; higher molecular weight grades generally undergo a greater percentage reduction in viscosity. Sterilization of solutions by gamma irradiation also results in a reduction in viscosity. Aqueous solutions stored for

prolonged periods should contain an antimicrobial preservative. The bulk material should be stored in a well-closed container in a cool, dry place.

11. Incompatibilities:

Carboxymethylcellulose sodium is incompatible with strongly acidic solutions and with the soluble salts of iron and some other metals, such as aluminum, mercury, and zinc. Precipitation may occur at pH <2, and also when it is mixed with ethanol (95%). Carboxymethylcellulose sodium forms complex coacervates with gelatin and pectin. It also forms a complex with collagen and is capable of precipitating certain positively charged proteins.

5.2.3. Xanthan Gum: *(Raymond C. R., et al., 2003)*

Nonproprietary Names:

BP **:** Xanthan gum

PhEur **:** Xanthani gummi

USPNF **:** Xanthan gum

Synonyms:

Corn sugar gum; E415; Keltrol; polysaccharide B-1459; Rhodigel; Vanzan NF; Xantural

Chemical name and CAS registry number:

Xanthan gum [11138-66-2]

Molecular weight:

Approximately 20,00,000.

Functional category:

Stabilizing agent; suspending agent and viscosity-increasing agent.

Description:

Xanthan gum occurs as a cream- or white-colored, odorless, free-flowing, fine powder.

Solubility:

It is practically insoluble in ethanol and ether, soluble in cold or warm water.

Viscosity (dynamic):

1200-1600 m Pa's (1200–1600 Cps) for 1% w/v aqueous solution at 25°C.

Applications in pharmaceutical formulation or technology:

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent. It is nontoxic, compatible with most other pharmaceutical ingredients, and has good stability and viscosity properties over a wide pH and temperature range. When xanthan gum is mixed with certain inorganic suspending agents, such as magnesium aluminum silicate, or organic gums, synergistic rheological effects occur. It is used as for preparation of sustained release matrix tablets and also used as thickening agent in shampoo.

Stability and storage conditions:

Bulk material should be stored in a well closed container in a cool, dry place.

5.2.4. Cellulose, Microcrystalline: *(Raymond C. R., et al., 2003)*

Nonproprietary names:

BP **:** Microcrystalline cellulose

JP **:** Microcrystalline cellulose

PhEur **:** Cellulosum microcristallinum

USPNF **:** Microcrystalline cellulose

Synonyms:

Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

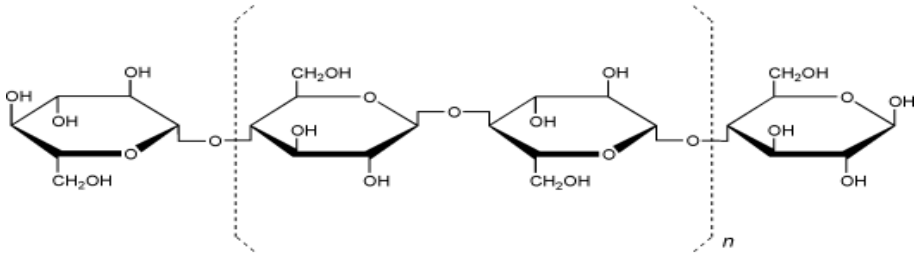
Chemical name and CAS registry number:

Cellulose [9004-34-6]

Molecular weight:

Approximately 36,000

Structural formula:



Functional category:

Adsorbent; suspending agent; tablet and capsule diluents; tablet disintegrant.

Description:

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous

particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Moisture content:

Typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.

Solubility:

Slightly soluble in 5% w/v sodium hydroxide solution, practically insoluble in water, dilute acids and most organic solvents.

Applications in pharmaceutical formulation or technology:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as binder/diluents in oral tablet and capsule formulations where it is used in both wet-granulation and direct compression processes. In addition to its use as binder/diluents, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

Stability and storage conditions:

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

5.2.5. Talc: *(Raymond C. R., et al., 2003)*

Nonproprietary names:

BP **:** Purified talc

JP **:** Talc

PhEur **:** Talcum

USPNF **:** Talc

Synonyms:

Purified chalk, altalc, powdered talc and soapstone

Chemical name and CAS registry number:

Talc [14807-96-6]

Description:

A very fine, white to grayish white, impalpable, odorless crystalline powder, Unctuous, adheres readily to skin, soft to touch and free from granules.

Empirical formula: $Mg_6 (Si_2O_5)_4(OH)_4$

Functional category:

Tablet, capsule it can use as a lubricant and diluents. During compression used as glidant and anticaking agent

Solubility **:** Insoluble in water, organic solvents, dilute acids and alkalis.

Storage conditions: Stable, Preserve in a well-closed container in a cool, dry place.

5.2.6. Magnesium stearate: *(Raymond C.R., et al., 2003)*

Nonproprietary names:

BP **:** Magnesium stearate

JP **:** Magnesium stearate

PhEur **:** Magnesii stearas

USPNF **:** Magnesium stearate

Synonyms **:** Magnesium octa decanoate, Magnesium salt.

Chemical name and CAS registry number:

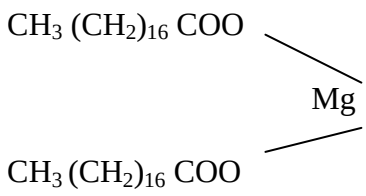
Octa decanoic acid magnesium salt [557-04-0]

Functional category **:** Tablet and capsule lubricant

Empirical formula **:** $C_{36}H_{70}MgO_4$

Molecular weight **:** 591.3

Structure **:**



Description:

It is a fine, white, precipitated or milled, impalpable powder of low bulk density and having a faint odor of stearic acid, characteristic taste.

Solubility:

It is insoluble in water, ethanol and ether. It can slightly soluble in warm ethanol and benzene.

Stability and storage conditions:

Stable, Store in a well closed container in a cool, dry place.

5.2.7. Povidone: *(Raymond C. R., et al., 2003)*

Nonproprietary names:

BP **:** Povidone

JP **:** Povidone

PhEur **:** Povidonum

USP **:** Povidone

Synonyms:

E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl) ethylene]; polyvidone; polyvinyl pyrrolidone; 1-vinyl-2-pyrrolidinone polymer.

Chemical name and CAS registry number:

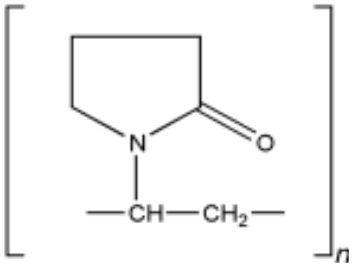
1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Empirical formula and molecular weight:

$(C_6H_9NO)_n$ and 2500-30,00,000 respectively

***K*-value**	**approximate molecular weight**
12	2500
15	8 000
25	30 000
30	50 000
60	400 000
90	1 000 000
120	3 000 000

Structural formula:



Functional category: Disintegrant; dissolution aid; suspending agent; tablet binder.

Description: Povidone occurs as a fine, white to creamy-white colored, odorless, hygroscopic powder.

Moisture content:

Povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidity.

Solubility:

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol and water; practically insoluble in ether, hydrocarbons and mineral oil.

Viscosity (dynamic):

The viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed.

Applications in pharmaceutical formulation or technology:

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet granulation processes. Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol or hydro alcoholic solutions.

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluents or coating agent	0.5–5

Stability and storage conditions:

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an aqueous solution does not alter its properties.

Materials & Equipments

6.MATERIALS AND EQUIPMENTS

Table 6.1: List of materials with source

S.No.	Name of Ingredients	Name of supplier
1	Aceclofenac	Tristar formulation Pvt. Ltd., Puducherry.
2	HPMC K15M	Tristar formulation Pvt. Ltd., Puducherry.
3	Carboxy methylcellulose	Tristar formulation Pvt. Ltd., Puducherry.
4	Xanthan gum	Nickon laboratories Pvt. Ltd., Puducherry.
5	Microcrystalline cellulose	Nickon laboratories Pvt. Ltd., Puducherry.
6	Polyvinyl pyrrolidone	Nickon laboratories Pvt. Ltd., Puducherry.
7	Magnesium stearate	Loba chemie Pvt.Ltd., Mumbai.
8	Talc	Loba chemie Pvt.Ltd., Mumbai.
9	Hydrochloric acid	S d fine-chem limited., Mumbai.
10	Methanol	Qualigens fine chemicals, Mumbai.
11	Acetone	Loba chemie Pvt.Ltd., Mumbai.
12	Sodium hydroxide	S d fine-chem limited., Mumbai.
13	Ethanol(95%)	S d fine-chem limited., Mumbai.
14	Chloroform	Loba chemie Pvt.Ltd., Mumbai.
15	Isopropyl alcohol	Qualigens fine chemicals, Mumbai.

6.2 Equipments used:

Table 6.2: List of equipments with model/make

S.No.	Equipment	Model/ Make
1	Electronic balance	Shimadzu BL-220H, Japan.
2	Bulk density apparatus	Indolabs VTAP/MATIC-II, Chennai.
3	Standard sieves	Jayant scientific, India.
4	Hot air oven	Precision scientific Co., Chennai.
5	Sixteen punch tablet compression machine	Cadmach, Ahmadabad, India.
6	Friability apparatus	Veego scientific VFT-DV, Mumbai.
7	Hardness tester	Monsanto
8	Vernier caliper	Indolabs, Mitutoyo.
9	Humidity chamber	Labtech, Ambala.
10	USP dissolution test apparatus Type I	Veego scientific VDA-8DR, Mumbai.
11	UV spectrophotometer	Elico-SL 159 UV-Visible spectrophotometer, Japan.
12	FTIR spectrophotometer	Perkin elmer-Pharmaspec-1.
13	Differential scanning calorimeter	Shimadzu DSC 60, Japan.

Experimental Work

7.EXPERIMENTAL WORK

7.1. PREFORMULATION STUDIES:

7.1.1. Characterization of Aceclofenac:

7.1.1.1. Organoleptic properties: *(Lachman L, et al., 1991; Banker G.S., and Rhodes C.T., 2009)*

The colour, odour and taste of the drug were recorded using descriptive terminology.

7.1.1.2. IR spectrum interpretation: *(IP, 2007; Silverstein R.M., Webster F.X., 2003)*

The infrared spectrum of pure Aceclofenac was recorded and spectral analysis was done. The dry sample of the drug was thoroughly mixed with potassium hydrobromide and directly placed in the sample holder.

7.1.1. Loss on drying: *(IP., 2007)*

Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified condition. The test can be carried out on the well mixed sample of the substance.

$$\text{Loss on drying} = \frac{\text{Initial weight of substance} - \text{Final weight of substance}}{\text{Initial weight of substance}} \times 100$$

7.1.1.4. Melting point: *(IP, 2007)*

Melting point of the drug was determined by capillary tube method.

7.1.1.5. Solubility study: *(IP, 2007)*

The solubility of drug was recorded by using various descriptive terminology specified in Indian Pharmacopoeia, 2007.

7.1.2. Analytical methods:

7.1.2.1. Determination of λ max: *(IP., 2007)*

Preparation of stock solution:

50 mg of Aceclofenac was accurately weighed and transferred to a 50 ml volumetric flask. It was dissolved in sufficient amount of Methanol and volume was made upto 50 ml with Methanol. Exactly 10ml of the stock solution was pipetted out and was diluted to 100 ml with Methanol (10 μg/ml). The spectrum was recorded in the range of 220-370 nm.

Preparation of standard curve of Aceclofenac: *(IP, 2007)*

i. By using in 0.1N hydrochloric acid:

A standard curve was prepared by dissolving 50 mg of Aceclofenac 50 ml of 0.1N HCl. In the stock solution 1 ml withdrawn and diluted to 25 ml of 0.1N HCl . It was further diluted with 0.1N HCl to get the solution in the concentration range of 0-20 μg/ml. The absorbance values were determined at 272.5 nm.

ii. By using in phosphate buffer p^H 7.4:

A standard curve was prepared by dissolving 50 mg of Aceclofenac in methanol and shake upto drug dissolved, then finally make upto 50 ml with pH 7.4 phosphate buffer. In the stock solution 1 ml withdrawn and diluted to 25 ml with phosphate buffer. It was further diluted to get the solution in the concentration range 0-20μg/ml. The absorbance values were determined at 274 nm.

7.1.3. Compatibility testing of drug with polymer: *(IP, 2007; Aulton M.E., 2007; Silverstein R.M, Webster F.X., 2003; Skoog D.A.,et.al.,1996)*

The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all drug substances and excipients to be used in the fabricating the product. Each polymer used in the formulations was blended with the drug levels that are realistic with respect to the final dosage form. Each polymer was thoroughly blended with drug to increase drug - polymer molecular contacts to accelerate the reactions if possible.

7.1.3. Fourier transform Infra-Red (FTIR) spectroscopy:

FTIR study was carried out to check compatibility of drug with polymers. Infrared spectrum of Aceclofenac was determined on Fourier transform Infrared Spectrophotometer using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run followed by drug with various polymers by using FTIR spectrophotometer. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum.

7.1.4. Differential scanning calorimetry (DSC):

Any possible drug polymer interaction can be studied by thermal analysis. The DSC study was performed on pure drug, and polymers, drug+HPMC K15M, drug+Carboxy methylcellulose and drug+ Xathan gum. The study was carried out using a Shimadzu. The 2 mg of sample were heated in a hermetically sealed aluminum pans in the temperature range of 25-300ºC at heating rate of 10ºC /min under nitrogen flow of 30ml/min.

7.1.4. Formulation of aceclofenac sustained release matrix tablets: *(Sharma A., et al., 2009; Bandhalarajan S., et al., 2011)*

Table 7.1: Composition of Aceclofenac matrix tablets

Ingredients(mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Aceclofenac	200	200	200	200	200	200	200	200	200
HPMC K15M	40	60	80	-	-	-	-	-	-
Carboxy methyl cellulose	-	-	-	40	60	80	-	-	-
Xanthan gum	-	-	-	-	-	-	40	60	80
Microcrystalline-cellulose	65	45	25	65	45	25	65	45	25
Polyvinyl pyrrolidone	30	30	30	30	30	30	30	30	30
Isopropyl alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Total weight	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

7.1.5. Preparation of granules: *(Prema R., et al., 2010)*

Granules for aceclofenac matrix tablets were prepared by wet granulation technique using various percentages of HPMC K15M, carboxy methyl cellulose and xanthan gum as release retardant polymers. All the powders passed through sieve No.80. The required quantity of drug, various polymers and other ingredients were mixed thoroughly and a sufficient volume of granulating agent (isopropyl alcoholic

solution of polyvinyl pyrrolidone) was added slowly. After enough cohesiveness was obtained, the wet mass was sieved through sieve No.8. The granules were dried at 60°C for 30 minutes and then the dried granules were passed through sieve No.16. Talc and magnesium stearate were finally added as a glidant and lubricant respectively.

7.1.6. Evaluation of granules:

7.1.6.1. Angle of repose: *(Subramanyam C.V.S., 2009)*

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the granules cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the granules cone respectively.

Table 7.2: Standard values of angle of repose (°)

S. No.	Flowability	Angle of repose
1	Excellent	<25
2	Good	25-30
3	Passable*	30-40
4	Poor	37-45
5	Very poor	>45

* Adding glidant for improving flow

7.1.6.2. Loose bulk density: *(Raghuram R. K., et al., 2003)*

An accurately weighed granules from each formulation was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the granules was measured which gave bulk volume. The loose bulk density of granules was determined using the following formula.

Loose bulk density = Total weight of granules / Total volume of granules

7.1.6.3. Tapped bulk density: *(Raghuram R.K., et al., 2003)*

An accurately weighed granules from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The TBD of granules was determined by the following formula.

Tapped bulk density = Total weight of granules/ Tapped volume

7.1.6.4. Hausner ratio: *(Aulton M.E., 2007)*

Hausner ratio is the ratio between tapped density and bulk density. Hausner ratio less than 1.25 indicates good flow properties while Hausner ratio greater than 1.25 shows poor flow of granules.

7.1.6.5. Carr's compressibility index: *(Aulton M.E., 2007)*

It is a simple index that can be determined on small quantities of granules. In theory, the less compressible a material the more flowable it is.

The compressibility index of the granules was determined using following formula.

Carr's compressibility index (%) = [(TBD-LBD)/ TBD] ×100

Table 7.3: Standard values of carr's index

Carr's index %	Flowability
5-15	Excellent
12-16	Good
18-21	Fairly acceptable
23-35	Poor
33-38	Very poor
< 40	Very very poor

7.2. Preparation of tablets: *(Bandhalarajan S., et al., 2011)*

The evaluation of granules showed excellent flow properties. The granules were compressed into tablets on 16 station rotary tablet compression machine using 11 mm round, biconcave punches. The compressed tablets were evaluated for various parameters viz. appearance, thickness, diameter, hardness, friability, weight variation, drug content and *in vitro* drug release studies.

7.3. Evaluation of Sustained release matrix tablet of Aceclofenac:

7.3.1. Appearance: *(Lachman L., et al., 1991; Bankar G.S. and Rhodes C.T., 2009)*

The tablets were visually observed for capping, chipping, and lamination.

7.3.2. Dimension (thickness and diameter): *(Lachman L., et al., 1991)*

The thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of the tablets was determined using a vernier caliper. Ten tablets from each type of formulation were used and average values were calculated.

7.3.3. Weight variation test: *(IP, 2007)*

For weight variation, 20 tablets of each type of formulation were weighed individually on an electronic balance, average weight was calculated and individual tablet weight was then compared with the average value to find out the deviation in weight.

Table 7.4: Specifications of %Weight variation allowed in tablets as per IP.

S. No	Average Weight of tablet	% Deviation
1.	80 mg or less	10
2	More than 80 but less than 250 mg	7.5
3	250 mg or more	5

7.3.4. Hardness:

For each type of formulation, the hardness value of 10 tablets was determined using Monsanto hardness tester.

7.3.5. Percentage friability : *(Lachman L., et al., 1991; Banker G.S. and Rhodes C.T., 2009)*

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated as follows,

$$\%F = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

7.3.6. Content uniformity: (*Krishna R. Gupta, et al., 2011*; *IP, 2007)*

Content uniformity was determined by accurately weighing 20 tablets and crushing them in mortar with the help of a pestle. Then an accurately weighed quantity of powder equivalent to 25 mg of drug was transferred to a 50 ml volumetric flask. Then added few ml of methanol and made upto 50ml with methanol. The solution was filtered through whatmann filter paper. 5 ml of the filtrate was diluted to 50 ml with Methanol. Then 3 ml of the resulting solution was again diluted to 10 ml with Methanol. The absorbance of the resulting 15 µg/ml solution was recorded at 274nm.

7.3.7. In-vitro dissolution studies: *(IP, 2007; Bandhalarajan S., et al., 2011; Yeole P.G., et al., 2006)*

The *in-vitro* dissolution studies were performed using USP type I dissolution apparatus at 50rpm. Dissolution test was carried out for a total period of 8 hours using 0.1N HCl (pH 1.2) solution (900 ml) as dissolution medium at 37 ± 0.5° for first 2 h, and pH 7.4 phosphate buffer solution (900 ml) for the rest of the period An aliquot (5ml) was withdrawn at specific time intervals and absorbance was determined by U.V. spectrophotometer at 274nm. The release studies were conducted in triplicate.

7.3.8. Data Analysis (Curve Fitting Analysis): *(Brahmankar D.M and Jaiswal S.B., 2009; Chandira, et al., 2009)*

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were graphed as:

i. Cumulative percentage drug released Vs Time (*In-vitro* drug release plots)

ii. Cumulative percentage drug released Vs Square root of time (Higuchi's plots)

iii. Log cumulative percentage drug remaining Vs Time (First order plots)

iv. Log percentage drug released Vs Log time (Peppas plots)

Higuchi release model:

To study the Higuchi release kinetics, the release rate data was fitted to the following equation. $F = K.t^{1/2}$

Where, 'F' is the amount of drug release,

'K' is the release rate constant, and 't' is the release time.

When the data is plotted as accumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

Korsmeyer and Peppas release model:

The release rate data were fitted to the following equation,

$$Mt / M\infty = K. t^n$$

Where, $Mt / M\infty$ is the fraction of drug release,

'K' is the release constant,

't' is the release time,

'n' is the diffusional exponent for the drug release that dependent on the shape of the matrix dosage form.

When the data is plotted as Log of released versus Log time, yields as straight line with a slope equal to 'n' and the 'K' can be obtained from Y – intercept.

For non- Fickian release the 'n' values falls between 0.5 and 1.0 while for Fickian (case I) diffusion n= 0.5 and zero order release (case II transport) n= 1.0.

Zero order release rate kinetics:

To study the zero-order release kinetics the release rate data are fitted to the following equation.

$$F = Kt$$

Where 'F' is the fraction of drug release,

'K' is the release rate constant and

't' is the release time.

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K.

7.4. Stability study: *(Carstensen J. T., et al., 2008; Manavalan R, et al., 2008)*

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted.

ICH specifies the length of study and storage conditions

- **Long-Term Testing**: 25°C ± 2°C at 60% RH ± 5% for 12 Months
- **Accelerated Testing:** 40°C ± 2°C at 75% RH ± 5% for 6 Months

In present study the selected formulation F9 exposure up to 3 months stability studies at accelerated condition (40°C ± 2°C at 75% RH ± 5% RH) to find out the effect of aging on hardness, drug content and *in vitro* drug release.

Stability studies were carried out at accelerated condition (40°C ± 2°C at 75% RH ± 5% RH) for the optimized formulation F9. The matrix tablets were stored at 40°C ± 2°C at 75% RH ± 5% RH for accelerated temperature in closely packed with aluminium foil for 3 months. The samples were withdrawn after periods of 1st month, 2nd month and 3rd month. The samples were analyzed for its hardness, drug content and *in vitro* drug release.

Results & Discussion

8. RESULTS AND DISCUSSION

8.1. Preformulation Parameters:

8.1.1. Characterization of Aceclofenac:

8.1.1.1. Organoleptic properties:

Odourless, white or almost white crystalline powder.

8.1.1.2. IR spectrum interpretation:

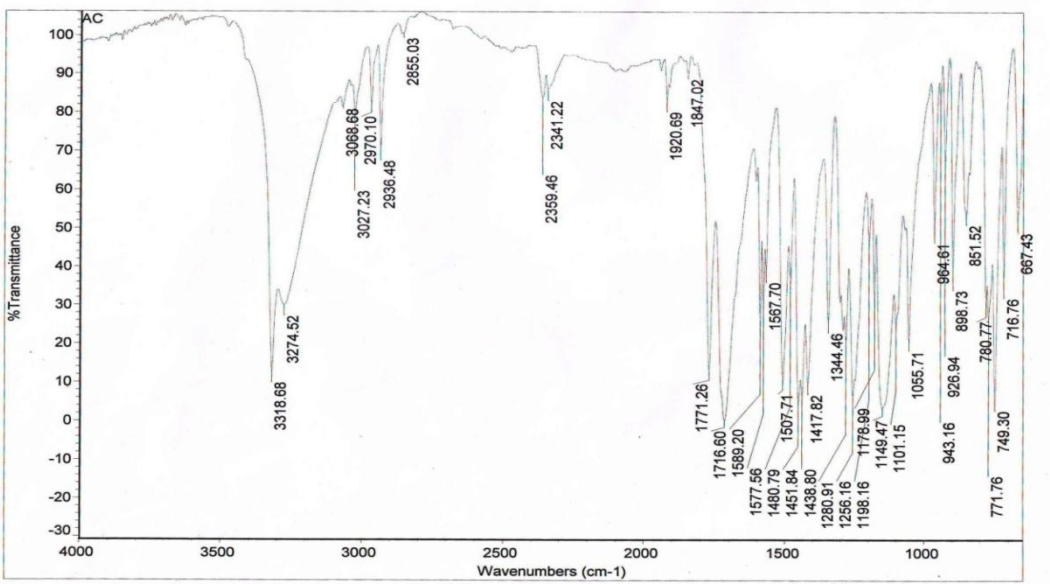


Figure 8.1: IR spectra of Aceclofenac

8.1.1.3. Loss on drying:

The percentage loss on drying for Aceclofenac was found to be 0.1%.

8.1.1.4. Melting point:

Melting point values of Aceclofenac sample was found to be 152^0C, 153^0C and 152^0C. The reported melting point Average for Aceclofenac is 152.33^0C. Hence, experimental values are in good agreement with official values.

8.1.1.5. Solubility study:

Table 8.1: Solubility of aceclofenac in different solvents

S.No.	Solvent used	Inference
1	Distilled water	insoluble
2	Ethanol 95%	soluble
3	Methanol	soluble
4	0.1N HCl	very slightly soluble
5	0.1N NaOH	insoluble
6	Acetone	freely soluble
7	pH 7.4 phosphate buffer	slightly soluble
8	Chloroform	sparingly soluble

8.1.2. λmax Determination:

8.1.2.1. λmax Determination in 0.1N HCl:

The absorption maximum for Aceclofenac was found to be 272.5 nm.

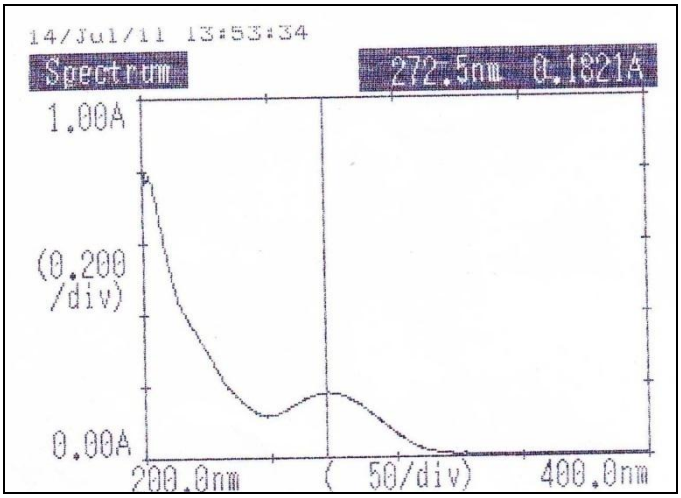


Figure 8.2: λ max observed for Aceclofenac in 0.1N HCl

8.1.2.2. λmax Determination in Phosphate buffer pH 7.4:

The absorption maximum for Aceclofenac was found to be 274 nm.

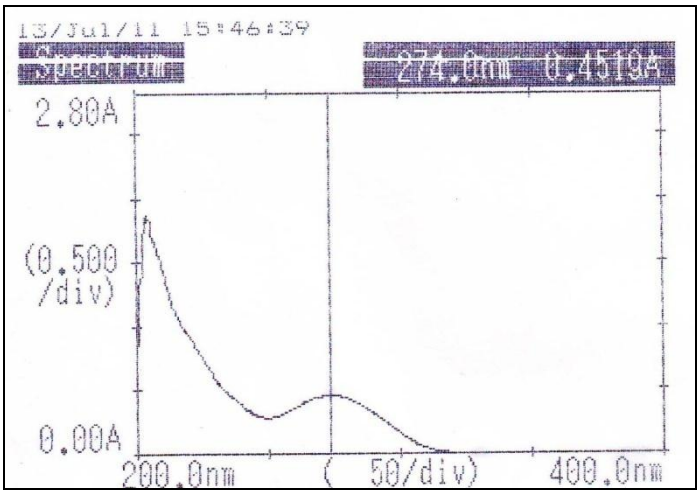


Figure 8.3: λ max observed for Aceclofenac in Phosphate buffer pH 7.4

8.1.2.3. Preparation of standard curve of Aceclofenac:

i. By using in 0.1N HCl:

UV absorption spectrum of Aceclofenac in 0.1N HCl shows λ max at 272.5 nm. Absorbance obtained for various concentrations of Aceclofenac 0.1N HCl in are given in table 8.2. The graph of absorbance vs. concentration for Aceclofenac was found to be linear in the concentration range of 4 – 20 µg /ml.

Table 8.2: Data of concentration and absorbance for Aceclofenac in 0.1N HCl

S.No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	4	0.061
3	8	0.124
4	12	0.183
5	16	0.245
6	20	0.306

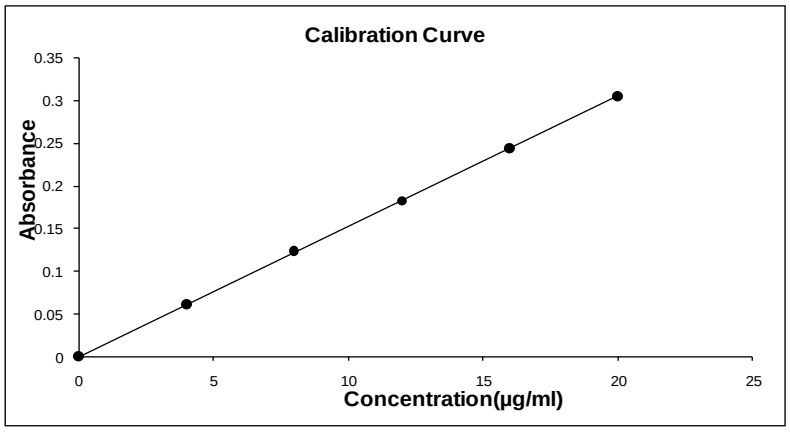


Figure 8.4: Calibration Curve of Aceclofenac in 0.1N HCl

Table 8.3: Data for Calibration Curve Parameter of 0.1N HCl

S.No.	Parameters	Values
1	Correlation coefficient (r)	0.9999
2	Slope	0.01529
3	Intercept	0.00024

ii. By using in Phosphate buffer pH 7.4:

UV absorption spectrum of Aceclofenac in Phosphate buffer pH 7.4 shows λ max at 275 nm. Absorbance obtained from various concentrations of Aceclofenac Phosphate buffer pH 7.4 is are given in table 8.4. The graph of absorbance *vs* concentration for Aceclofenac was found to be linear in the concentration range of 4 – 20 µg/ml.

Table 8.4: Concentration and absorbance for Aceclofenac in Phosphate buffer pH 7.4

S. No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	4	0.146
3	8	0.291
4	12	0.432
5	16	0.575
6	20	0.715

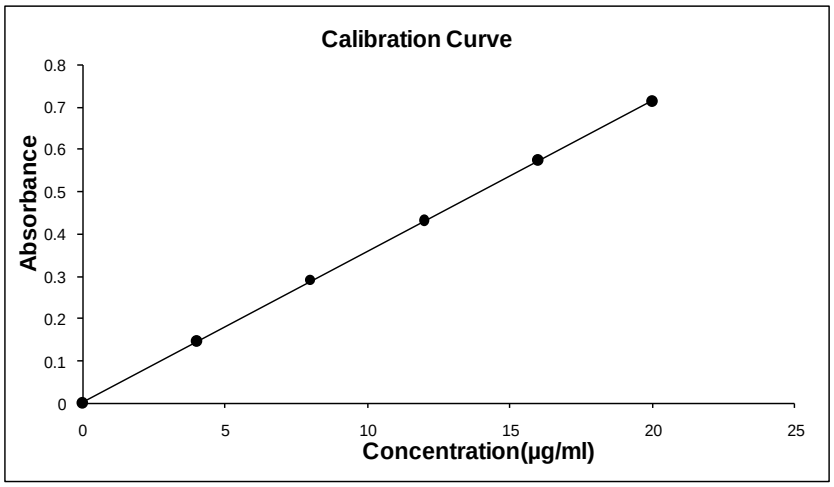


Figure 8.5: Calibration curve of Aceclofenac in Phosphate buffer pH 7.4

Table 8.5: Data for Calibration Curve Parameter of Phosphate buffer pH 7.4

S.No.	Parameters	Values
1	Correlation coefficient (r)	0.9999
2	Slope	0.03574
3	Intercept	0.00248

8.1.2.4. Percentage purity of pure Drug:

The percentage purity of drug was calculated by using calibration graph method (least square method).

Table 8.6: Percentage purity of pure drug

S.No.	Percentage purity (%)	Avg. percentage purity (%)
1	98.32	99.69±1.21
2	100.16	
3	100.60	

The reported percentage purity for Aceclofenac is 99 to 101% (Indian Pharmacopoeia 2007).

8.1.3. Compatibility testing of drug with polymer:

8.1.3.1. Fourier transform Infra-Red (FTIR) spectra's:

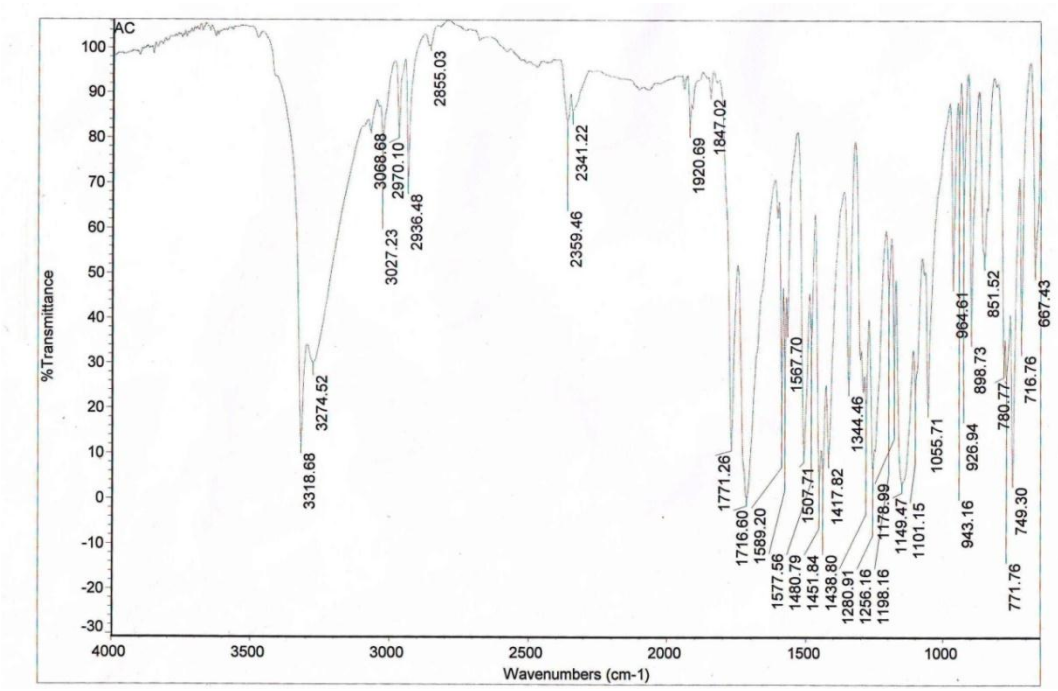


Figure 8.6: IR spectra of Aceclofenac

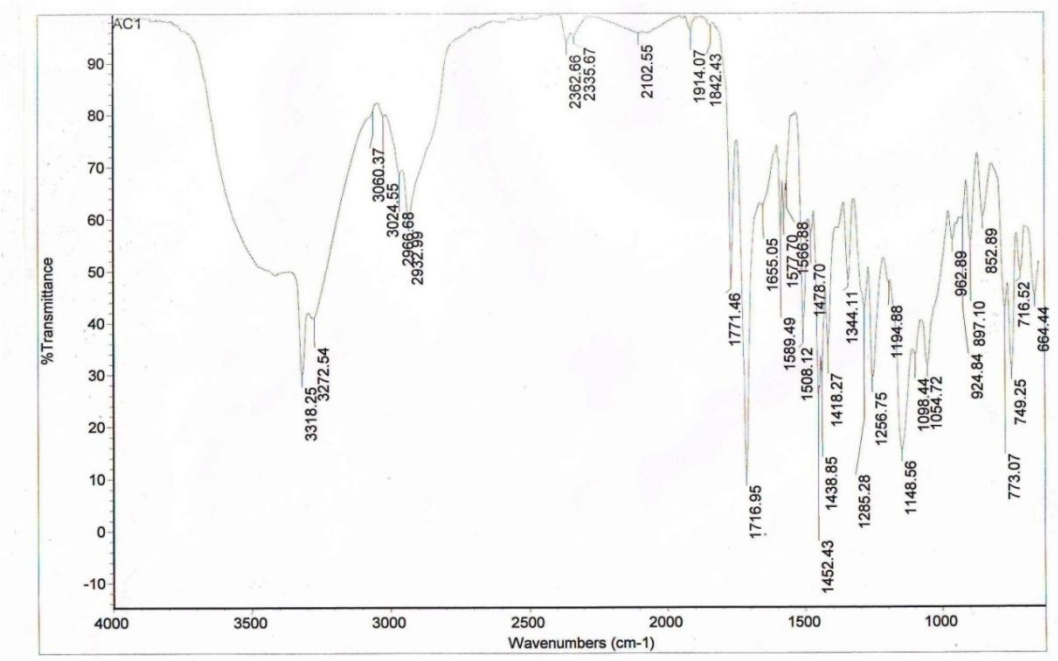


Figure 8.7: IR spectra of Aceclofenac and HPMC K15M

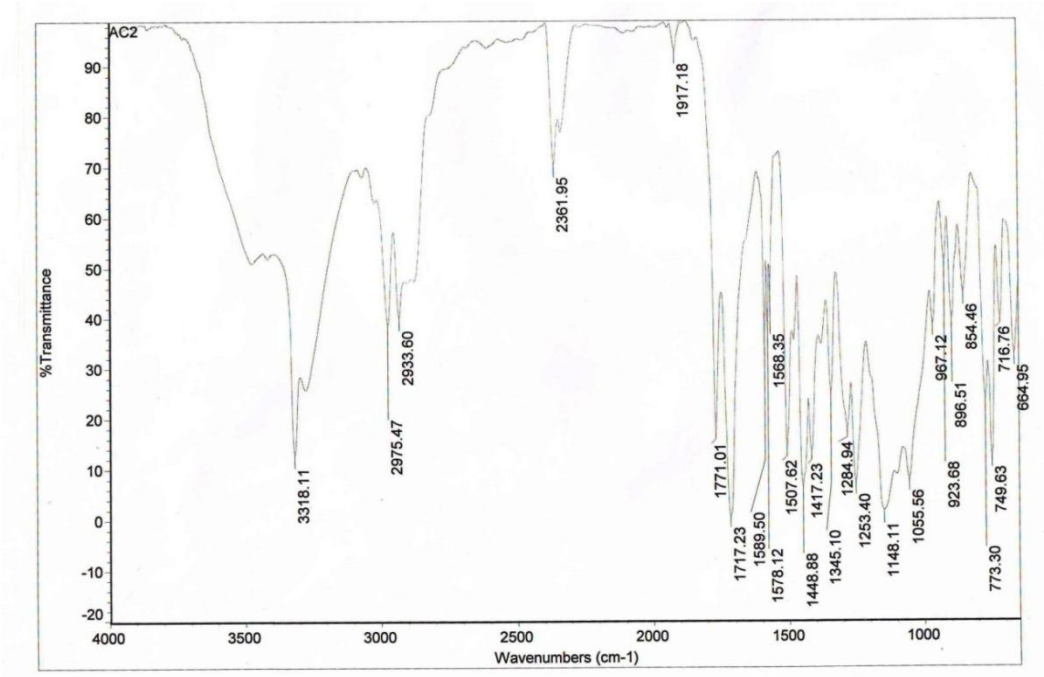


Figure 8.8: IR spectra of Aceclofenac and Carboxy methyl cellulose

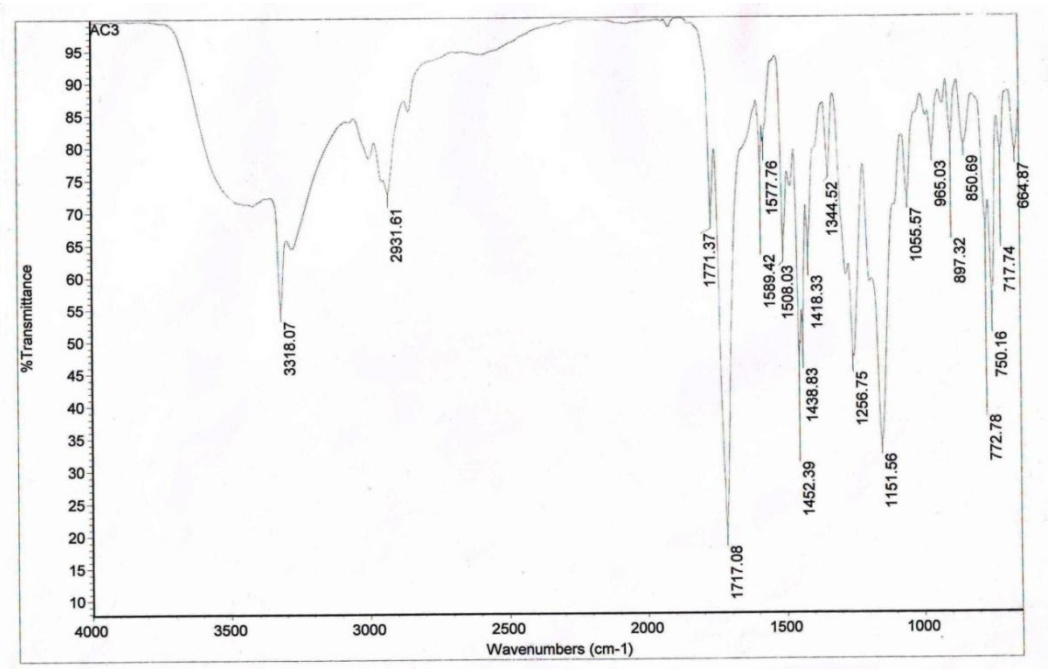


Figure 8.9: IR spectra of Aceclofenac and Xanthan gum

FTIR spectroscopy was used to ensure that no chemical interaction between the drugs and polymers had occurred. From the FTIR spectral Figures 8.6 to 8.9 interpretations the following result was obtained. The FTIR of Aceclofenac and combination of polymers shows intense band in the table as follows.

Table 8.7: IR peaks of functional groups (cm^{-1})

Sr. No	Name of the ingredient	-C = O	-COOH	-NH	-OH
1.	Aceclofenac	1149.47	1771.26	1589.20	1055.71
2.	Aceclofenac and HPMC K15M	1148.56	1771.46	1589.49	1054.72
3.	Aceclofenac and Carboxy methyl cellulose	1148.11	1771.01	1589.50	1055.56
4.	Aceclofenac and Xanthan gum	1151.56	1771.37	1589.42	1055.57

8.1.3.2. Differential Scanning Calorimetry (DSC):

The compatibility and interactions between drugs and polymer were checked using DSC, results obtained were shown in Figure 8.10 to 8.13.

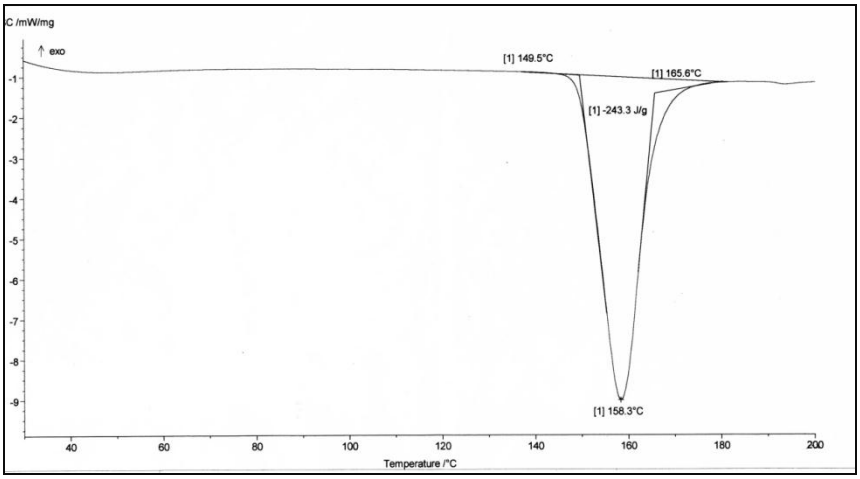


Figure 8.10: Differential Scanning Calorimetry analysis of Aceclofenac.

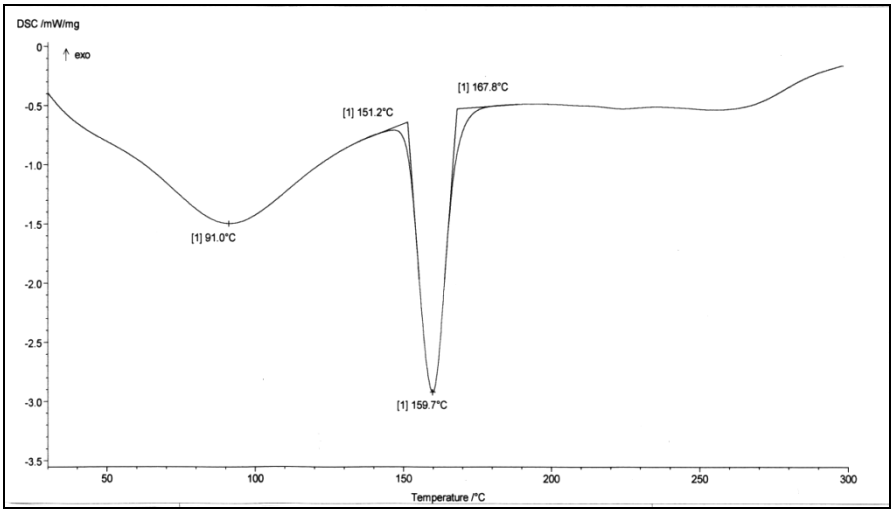


Figure 8.11: Differential Scanning Calorimetry Analysis of Aceclofenac and HPMC K15M.

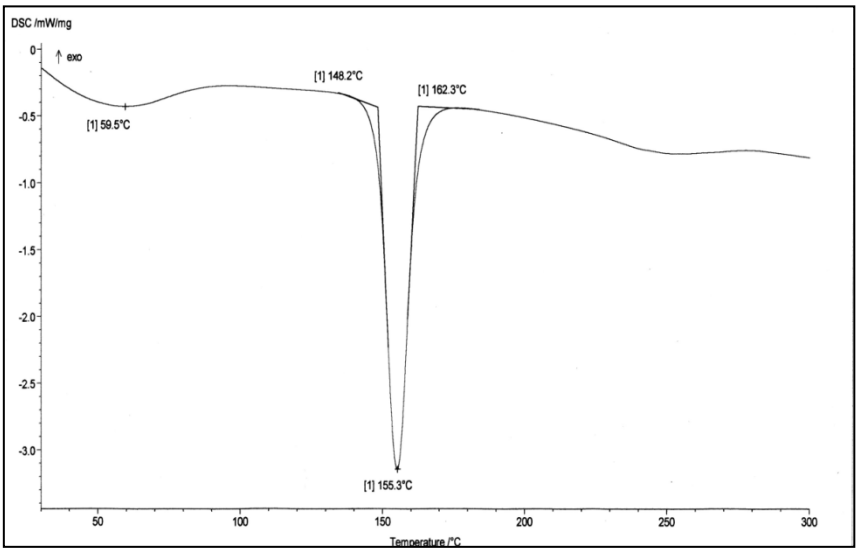


Figure 8.12: Differential Scanning Calorimetry Analysis of Aceclofenac and Carboxy methyl cellulose.

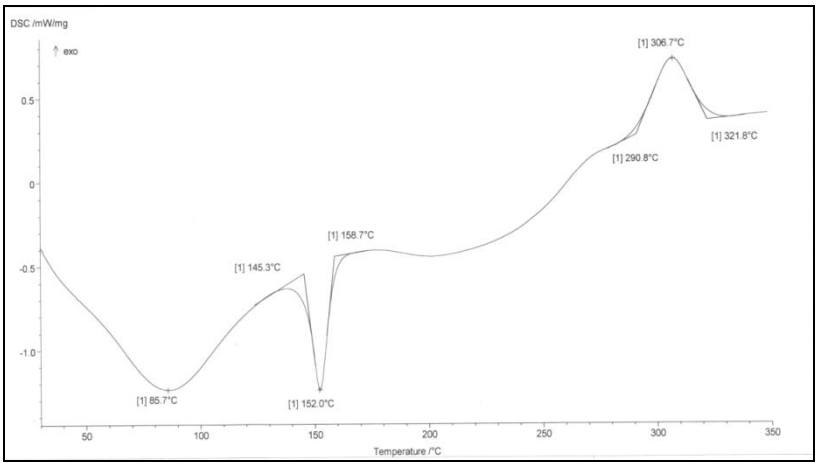


Figure 8.13: Differential Scanning Calorimetry Analysis of Aceclofenac and Xanthan gum.

Table 8.8: Data of DSC thermogram parameters

S.No.	Name of ingredients and physical mixtures used in formulation	Temperature at which peak obtained
1.	Aceclofenac	158.3^0C
2.	Aceclofenac and HPMC K15M	158.7^0C
3.	Aceclofenac and Carboxy methyl cellulose	155.3^0C
4.	Aceclofenac and Xanthan gum	152^0C

DSC thermogram showed that there was no any major difference in onset temperature and peak temperature, when compared with pure drug's thermogram interaction was found between drug and polymers.

8.2. Evaluation of blended granules:

The blended granules of different formulation were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner ratio. The results of these evaluations were as follows: -

8.2.1. Angle of repose:

Angle of repose ranged from 21.52° ± 1.03 to 24.92° ± 0.78. The results were found to be below 25° and hence the blend was found to have excellent flowability. (Table 8.9).

8.2.2. Loose bulk density and tapped density:

Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.455 ± 0.00 to 0.500 ± 0.00 g/ml; and 0.526 ± 0.00 to 0.588 ± 0.00 g/ml respectively. (Table 8.9).

Table 8.9: Flow properties of granules

Formulation code	Angle of repose (°)*	Loose bulk density (g/ml)*	Tapped bulk density (g/ml)*	Hausner's ratio*	Carr's index (%)*
F1	21.52±1.03	0.476±0.00	0.556±0.00	1.17±0.00	14.286±0.00
F2	22.34±0.49	0.500±0.00	0.588±0.00	1.18±0.00	15.000±0.00
F3	24.72±0.51	0.455±0.00	0.526±0.00	1.16±0.00	13.636±0.00
F4	24.92±0.78	0.500±0.00	0.588±0.00	1.18±0.00	15.000±0.00
F5	22.27±2.30	0.476±0.00	0.556±0.00	1.17±0.00	14.286±0.00
F6	24.04±1.62	0.476±0.00	0.556±0.00	1.17±0.00	14.286±0.00
F7	24.72±0.51	0.500±0.00	0.588±0.00	1.18±0.00	15.000±0.00
F8	24.04±1.62	0.455±0.00	0.526±0.00	1.16±0.00	13.636±0.00
F9	22.42±2.40	0.500±0.00	0.588±0.00	1.18±0.00	15.000±0.00

*All the values are expressed as mean± SE, n=3.

8.2.3. Compressibility index (Carr's index):

The compressibility index (%) ranged from 13.636 ± 0.00 to 15.000 ± 0.00 (Table 8.9). The blend was found to have excellent flowing property as the result were found to be below 15%.

8.2.4. Hausner ratio:

The Hausner ratio ranged from 1.16 ± 0.00 to 1.18 ± 0.00, (Table 8.9). The result indicates the free flowing properties of the granules.

8.3. Evaluation of sustanied release matrix tablets:

8.3.1. Appearance:

The tablets were observed visually and did not show any defect such as capping, chipping and lamination.

8.3.2. Physical characteristics:

The physical characteristic of Aceclofenac sustained release matrix tablets (F1 to F9) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and results of the formulations (F1 to F9) found to be within the limits specified in official books.

8.3.3. Dimension (Thickness and Diameter):

Thickness and diameter specifications may be set on an individual product basis. Excessive variation in the tablet thickness and diameter can result in problems with packaging as well as consumer acceptance. The size (diameter) of the tablets of all formulations was found to be 4.39±0.06 to 4.48±0.08 mm.

8.3.4. Tablet Hardness:

A difference in tablet hardness reflects difference in tablet density and porosity. In which turn are supposed to result in different release pattern of the drug

by affecting the rate of penetration of dissolution fluid at the surface of the tablet and formation of gel barrier. The hardness of tablets was found to be in the range of 7.65±0.58 kg/cm^2 to 8.05±0.50kg/cm^2. This indicates good tablet strength.

8.3.5. Percent Friability:

Percentage friability of all the formulations was found between 0.043 to 0.100%. This indicated good handling property of the prepared SR tablet.

8.3.6. Weight Variation:

A tablet is designed to contain a specific amount of drug. When the average mass of the tablet is 350 mg the pharmacopoeial limit for percentage deviation is ± 5 %. The percentage deviation from average tablet weight for all the tablet was found to be within the specified limits and hence all formulations complied with the test for weight variation according to the pharmacopeial specifications.

Table 8.10: Physico-Chemical Characterization of Aceclofenac SR Tablets

F. Code	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Weight variation (mg)	Drug content (%w/w)**
F1	4.42±0.06	7.80±0.59	0.057	351.40±2.26	99.48±0.45
F2	4.41±0.04	7.75±0.63	0.071	352.15±2.92	99.22±0.56
F3	4.42±0.07	7.70±0.54	0.085	350.10±2.77	99.61±0.69
F4	4.48±0.08	8.05±0.50	0.100	352.05±2.39	100.21±1.09
F5	4.39±0.06	7.85±0.34	0.057	353.05±2.84	99.78±1.05
F6	4.41±0.02	7.65±0.58	0.071	351.55±3.02	99.83±1.41
F7	4.44±0.08	7.80±0.48	0.071	352.60±2.39	100.61±0.35
F8	4.43±0.07	7.95±0.55	0.043	352.75±2.92	99.88±0.87
F9	4.46±0.02	7.85±0.41	0.043	351.75±2.95	98.90±0.65

*All the values are expressed as mean± SE, n=3

8.3.7. Drug content of Aceclofenac:

The content of active ingredients in the formulation was found to be between 98.90±0.65 to 100.61±0.35 % w/w, which is within the specified limit as per Indian Pharmacopoeia 1996 (i.e. 90-110% w/w).

8.3.8. *In-Vitro* Dissolution Studies:

Table 8.11: *In-vitro* release drug profile of formulation F1

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	08.07±1.03	16.14	4.00	0.50
2	15.13±0.90	30.26	7.75	0.97
3	27.85±0.57	55.70	12.27	1.67
4	43.80±1.59	87.60	18.14	2.35
5	58.16±0.82	116.32	24.71	2.87
6	74.15±1.64	148.30	31.61	3.44
7	88.21±1.20	176.42	38.69	3.93
8	99.25±0.77	198.50	45.59	4.34

*****All values are expressed as mean ±SD, n=3.

Table 8.12: *In-vitro* release drug profile of formulation F2

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	07.19±0.74	14.37	3.54	0.50
2	14.64±1.06	29.28	7.21	1.02
3	25.25±0.33	50.50	11.36	1.62
4	40.07±1.07	80.13	16.54	2.33
5	55.89±0.69	111.78	22.68	2.93
6	71.04±1.29	142.09	29.39	3.52
7	85.06±2.12	170.13	36.36	4.02
8	96.61±0.98	193.21	43.16	4.41

*****All values are expressed as mean ±SD, n=3.

Table 8.13: *In-vitro* release drug profile of formulation F3

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	06.21±0.61	12.41	3.09	0.50
2	12.19±0.90	24.38	6.38	1.03
3	24.12±0.38	48.23	10.34	1.67
4	39.44±0.63	78.87	15.55	2.40
5	53.63±0.44	107.25	21.67	2.97
6	70.67±1.42	141.33	28.37	3.58
7	82.80±0.88	165.60	35.25	4.01
8	92.41±0.57	184.82	41.74	4.36

*****All values are expressed as mean ±SD, n=3.

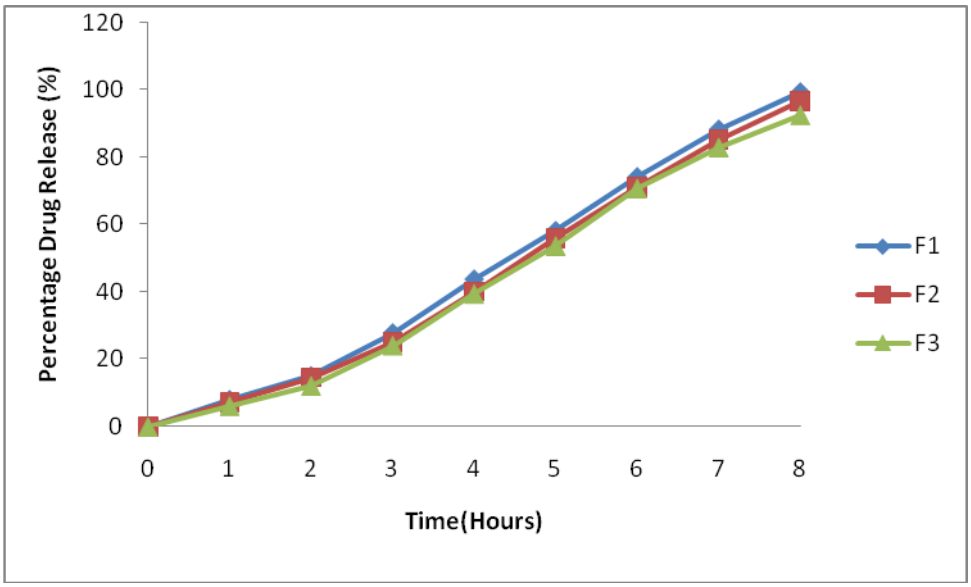


Figure 8.14: *In-vitro* Drug Release profile curve of formulations F1 to F3

Table 8.14: *In-vitro* release drug profile of formulation F4

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	09.25±1.51	18.49	4.61	0.50
2	16.11±1.06	32.22	8.66	0.93
3	25.84±0.38	51.67	12.71	1.50
4	41.03±0.44	82.06	17.81	2.25
5	54.63±0.38	109.27	23.75	2.81
6	70.04±0.57	140.07	30.21	3.44
7	86.41±0.51	172.81	37.15	4.00
8	96.82±0.57	193.63	44.01	4.38

***All values are expressed as mean ±SD, n=3.

Table 8.15: *In-vitro* release drug profile of formulation F5

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	07.48±1.03	14.96	3.49	0.50
2	14.15±1.19	28.30	7.04	1.01
3	23.61±0.25	47.22	10.92	1.59
4	39.44±0.72	78.87	15.98	2.37
5	52.79±0.38	105.57	21.97	2.91
6	69.83±0.58	139.66	28.53	3.55
7	84.64±0.32	169.29	35.52	4.07
8	92.28±0.82	184.57	42.18	4.36

*****All values are expressed as mean ±SD, n=3.

Table 8.16: *In-vitro* release drug profile of formulation F6

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	06.11±0.88	12.21	3.04	0.50
2	13.07±1.19	26.14	6.30	1.03
3	22.77±0.63	45.54	10.09	1.64
4	38.89±0.44	77.78	15.17	2.43
5	47.33±0.51	94.65	20.72	2.80
6	66.05±0.50	132.10	26.70	3.58
7	81.24±0.63	162.49	33.43	4.13
8	89.05±0.51	178.10	39.94	4.43

*****All values are expressed as mean ±SD, n=3.

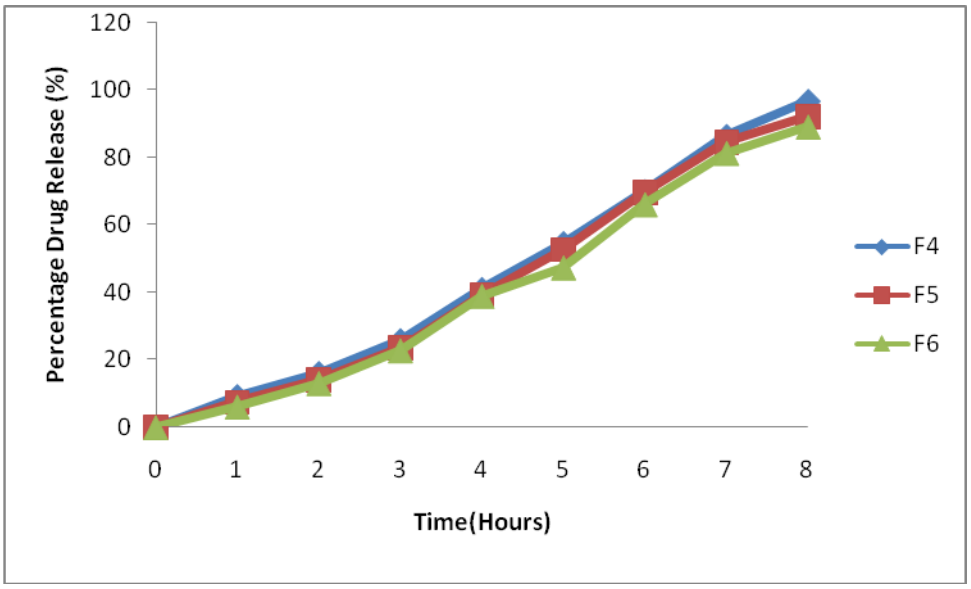


Figure 8.15: *In-vitro* Drug Release profile curve of formulations F4 to F6

Table 8.17: *In-vitro* release drug profile of formulation F7

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	08.17±0.88	16.33	4.05	0.50
2	15.03±0.90	30.07	7.82	0.96
3	24.29±0.38	48.57	11.80	1.55
4	37.76±0.63	75.51	16.58	2.23
5	49.47±0.51	98.94	21.94	2.78
6	62.65±0.83	125.30	27.62	3.36
7	78.77±0.45	157.54	33.79	4.01
8	91.49±0.50	182.97	40.24	4.49

***All values are expressed as mean ±SD, n=3.

Table 8.18: *In-vitro* release drug profile of formulation F8

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	06.50±0.90	13.00	3.24	0.50
2	13.37±1.03	26.73	6.58	1.02
3	21.60±0.83	43.19	10.24	1.59
4	31.38±0.76	62.75	14.28	2.16
5	46.74±0.32	93.48	19.18	2.94
6	58.45±0.84	116.90	24.73	3.46
7	75.03±0.57	150.06	30.74	4.14
8	87.67±0.44	175.33	37.10	4.63

*****All values are expressed as mean ±SD, n=3.

Table 8.19: *In-vitro* release drug profile of formulation F9

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	05.33±0.74	10.64	2.63	0.50
2	12.29±1.18	24.57	5.72	1.07
3	19.79±1.27	39.58	9.20	1.62
4	28.40±0.58	56.79	12.90	2.16
5	35.58±0.38	71.15	16.65	2.64
6	47.25±0.69	94.49	20.73	3.36
7	61.43±0.51	122.87	25.52	4.09
8	78.31±0.38	156.61	31.08	4.84

*****All values are expressed as mean ±SD, n=3.

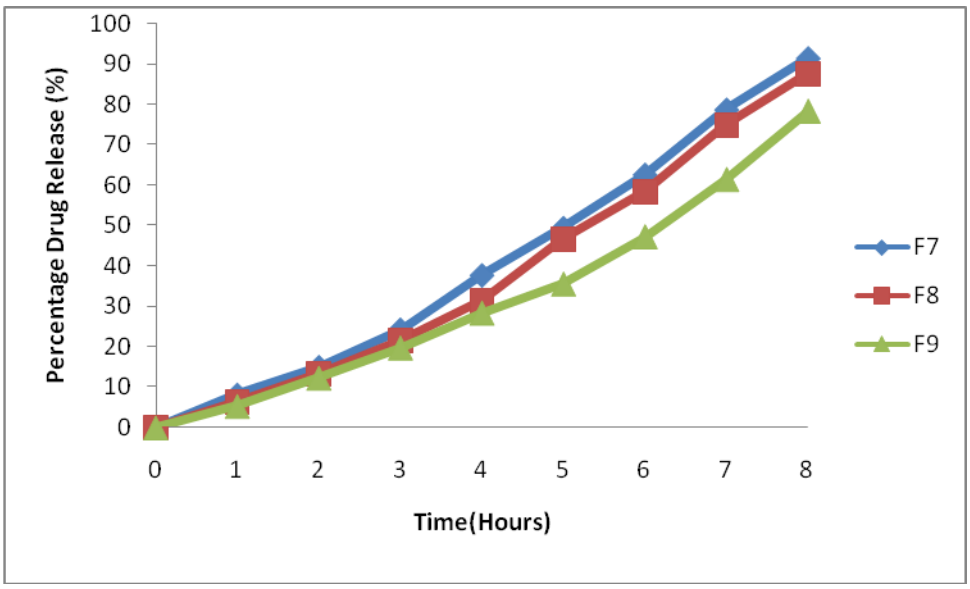


Figure 8.16: *In-vitro* Drug Release profile curve of formulations F7 to F9

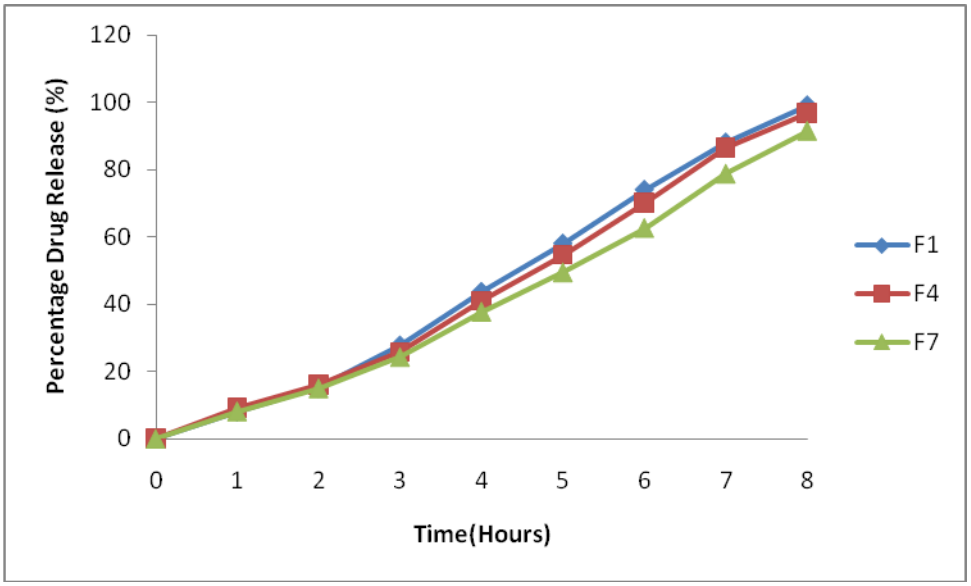


Figure 8.17: *In-vitro* Drug Release profile curve for different polymers at 20%concentration of formulations F1, F4 and F7.

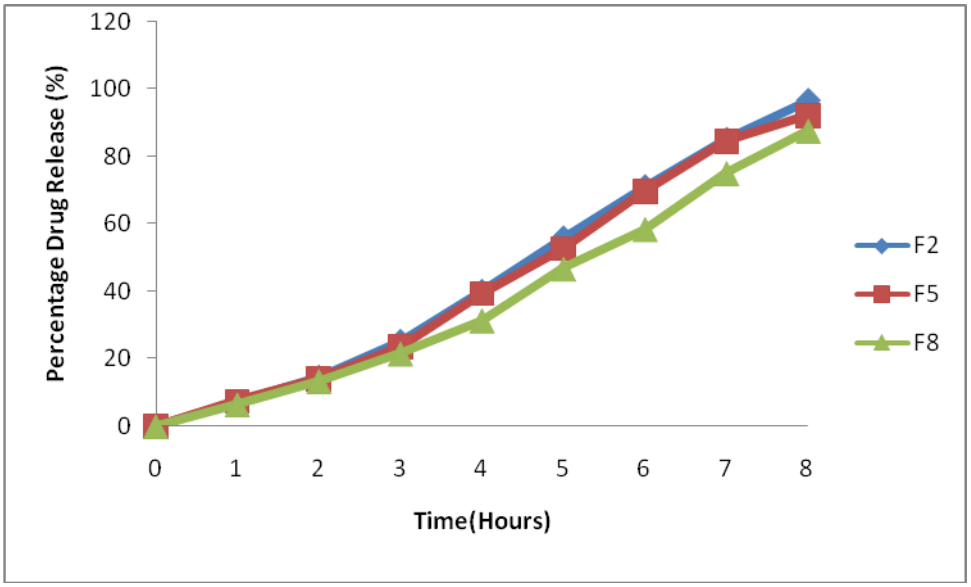


Figure 8.18: *In-vitro* Drug Release profile curve for different polymers at 30% concentration of formulations F2, F5 and F8.

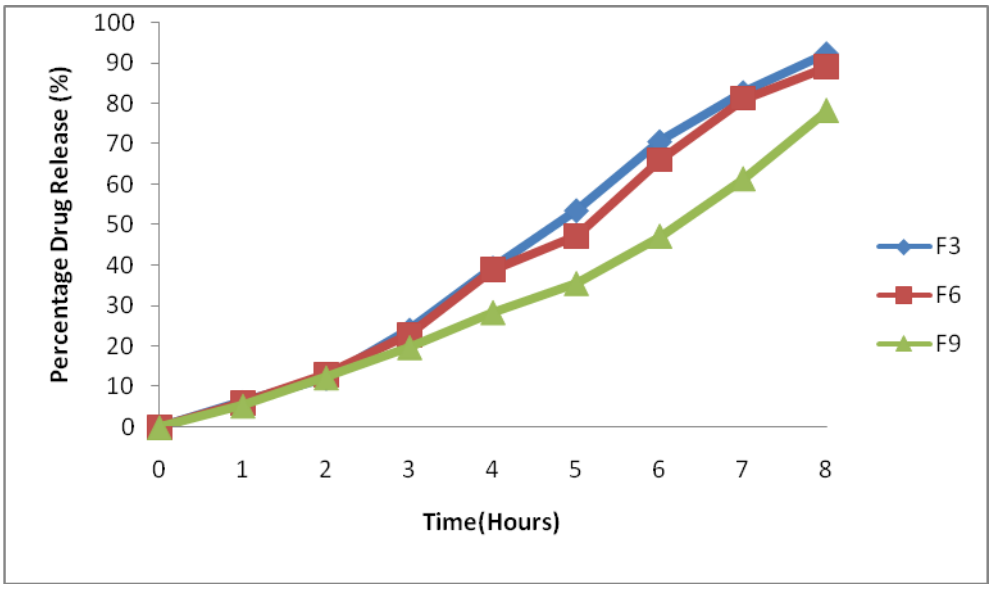


Figure 8.19: *In-vitro* Drug Release profile curve for different polymers at 40% concentration of formulations F3, F6 and F9.

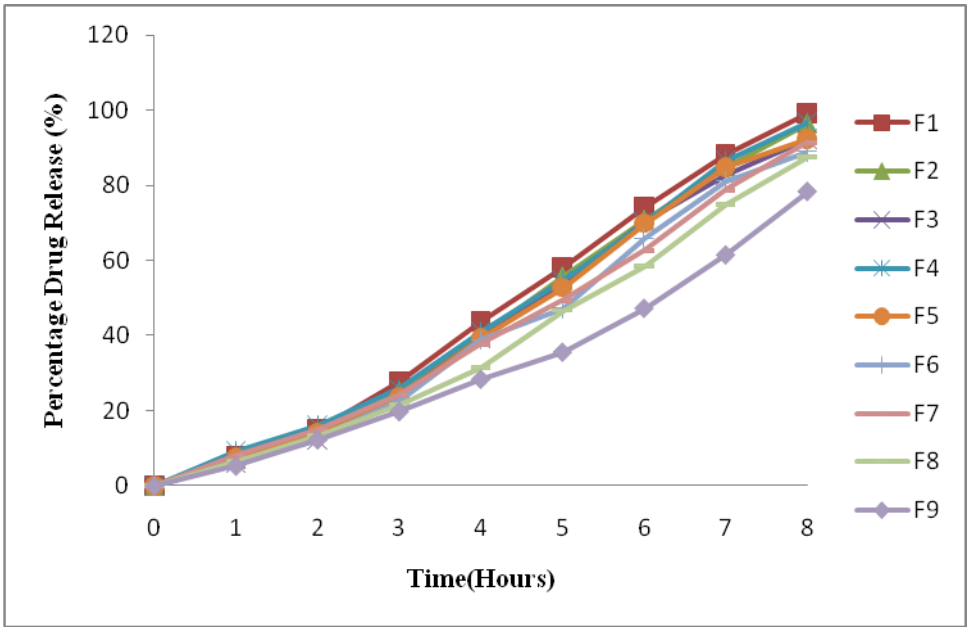


Figure 8.20: Comparative study of Cumulative *In-vitro* % drug release curve of formulation F1 *to* F9.

Table 8.20: Time of *in vitro* drug released for aceclofenac $t_{50\%}$ values of F1 to F9.

Formulation code	**Time of drug released (hours) ($t_{50\%}$)**
F1	4.4
F2	4.6
F3	4.8
F4	4.7
F5	4.8
F6	5.2
F7	5.1
F8	5.3
F9	6.2

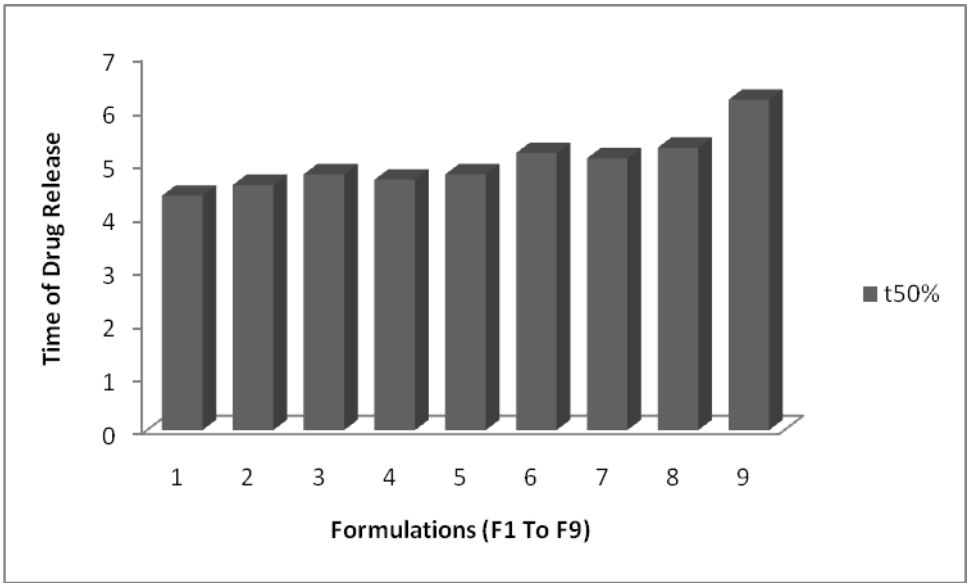


Figure 8.21: *In vitro* drug release for $t_{50\%}$ values of F1 to F9.

Aceclofenac is a water insoluble drug; its release from the matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. The concentration of polymer in the sustained release layer was a key factor in controlling the drug release. Various sustained release formulations were formulated with HPMC K15M, Carboxy methyl cellulose, Xanthan gum polymer alone; polyvinyl pyrrolidone as binder and microcrystalline cellulose was used as diluents.

In vitro release studies of formulations F1, F2 and F3 prepared by HPMC K15M with concentrations of 20%, 30% & 40% respectively. The drug released from formulation F1 to F3 were found to be 99.25 ± 0.77, 96.61 ± 0.98, and 92.41 ± 0.57% for aceclofenac respectively.

In vitro release studies of formulations F4, F5 and F6 prepared by Carboxy methyl cellulose with concentrations of 20%, 30%& 40% respectively. The drug released from formulation F4 to F6 were found to be 96.82 ± 0.57, 92.28 ± 0.82, and 89.05 ± 0.51% for aceclofenac respectively.

In vitro release studies of formulations F7, F8 and F9 prepared by Xanthan gum with concentrations of 20%, 30%& 40% respectively. The drug released from formulation F7 to F9 were found to be 91.49 ± 0.50, 87.67 ± 0.44, and 78.31 ± 0.38% for aceclofenac respectively.

The release rate of F9 was found to be higher when compared to other formulations this is due to increase in the concentration of polymer (Xanthan gum).

In vitro release studies of formulations F3, F6 and F9 prepared by with concentrations of 30% HPMC K15M, Carboxy methyl cellulose and Xanthan gum shows sustained release effects.

The result of $t_{50\%}$ was shown in Table 8.20 and Figure 8.21, according to the time of drug release values of $t_{50\%}$, the formulation F9 was selected as the best formulation.

The overall release rate of aceclofenac from carboxy methyl cellulose and HPMC K15M matrices are significantly higher than that from xanthan gum matrices; were shown in Figure 8.20 and which is confirmed by smaller MDT (4.38, 4.36, 4.43 and 4.34, 4.41, 4.36) respectively for carboxy methyl cellulose and HPMC K15M and higher MDT for xanthan gum matrices. These results are indicating that xanthan gum has higher drug retarding ability for long duration than carboxy methyl cellulose and HPMC K15M. Xanthan gum also showed the least %DE while carboxy methyl cellulose and HPMC K15M also showed the greatest %DE among the tablets with just one of the retarding polymers.

Based on the *in-vitro* drug release data, MDT, %DE and $t_{50\%}$, the formulation F9 was selected as the optimized formulation. Hence the formulation F9 was selected for the further stability study.

8.3.9. Data Analysis (Curve Fitting Analysis):

Korsemeyer-Peppas model indicates that the release mechanism is not well known or more than one type of release phenomena could be involved. The 'n' value could be used to characterize different release mechanisms as:

Table 8.21: Different drug release mechanisms of kinetic model

Release exponent (n)	Drug Transport Mechanism
0.5	Fickian diffusion
0.45< n=0.89	Non- Fickian diffusion
0.89	Case II transport
Higher than 0.89	Super case II transport

It ranges between 0.5 to 1, so it was concluded that the drug release occurred via non-fickian diffusion, which shows that the release from initially dry, hydrophilic glassy polymers that swell when added to water and become rubbery show anomalous diffusion as a result of the rearrangement of macro molecular chains.

8.3.2.8. Kinetic studies:

Table 8.22: In-vitro Release Kinetic models for Aceclofenac sustained release Matrix tablets of formulations (F1 to F9)

F. Code	Zero order	First order	Higuchi	Korsemeyer- Peppas		Best fit model
	R^2	R^2	R^2	R^2	Slope(n)	
F1	0.989	0.623	0.857	0.992	1.268	Peppas
F2	0.986	0.725	0.846	0.994	1.302	Peppas
F3	0.984	0.805	0.842	0.991	1.376	Peppas
F4	0.986	0.719	0.850	0.987	1.186	Peppas
F5	0.983	0.803	0.843	0.989	1.279	Peppas
F6	0.981	0.817	0.838	0.994	1.342	Peppas
F7	0.986	0.778	0.846	0.991	1.197	Peppas
F8	0.977	0.792	0.825	0.993	1.279	Peppas
F9	0.967	0.803	0.813	0.995	1.262	Peppas

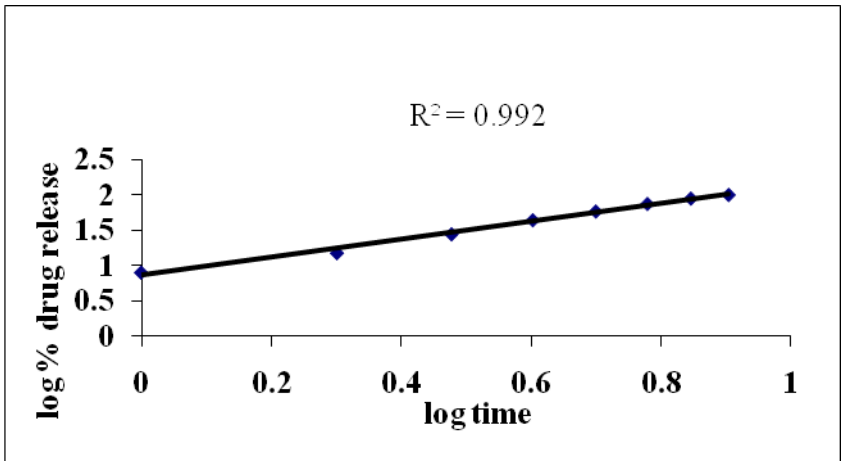


Figure 8.22: Best fit model (Peppas) of formulation F1

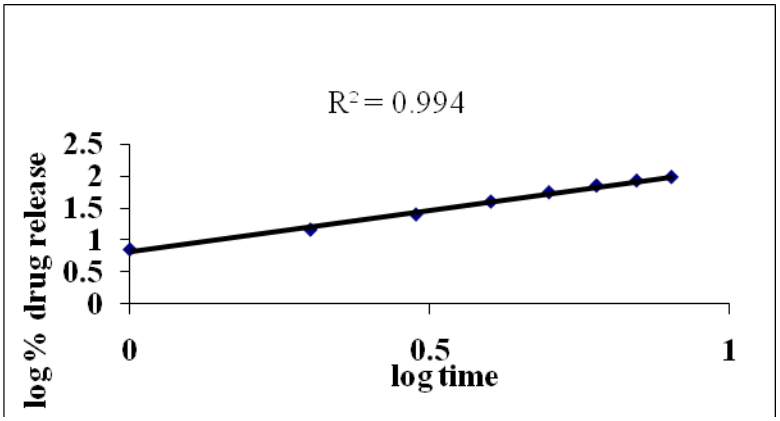


Figure 8.23: Best fit model (Peppas) of formulation F2

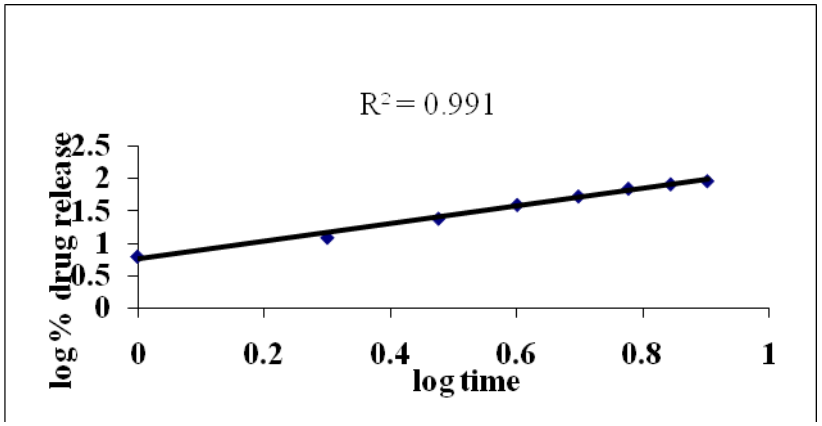


Figure 8.24: Best fit model (Peppas) of formulation F3

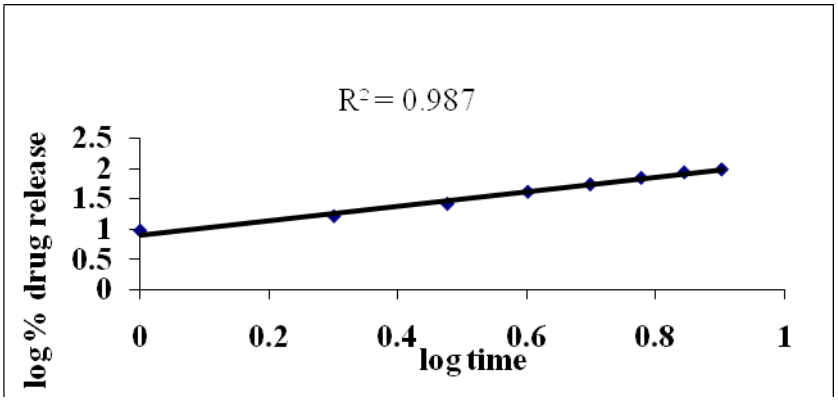


Figure 8.25: Best fit model (Peppas) of formulation F4

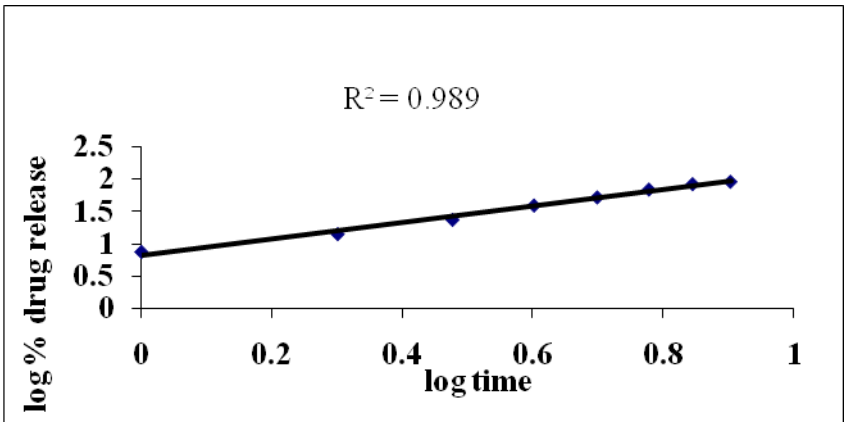


Figure 8.26: Best fit model (Peppas) of formulation F5

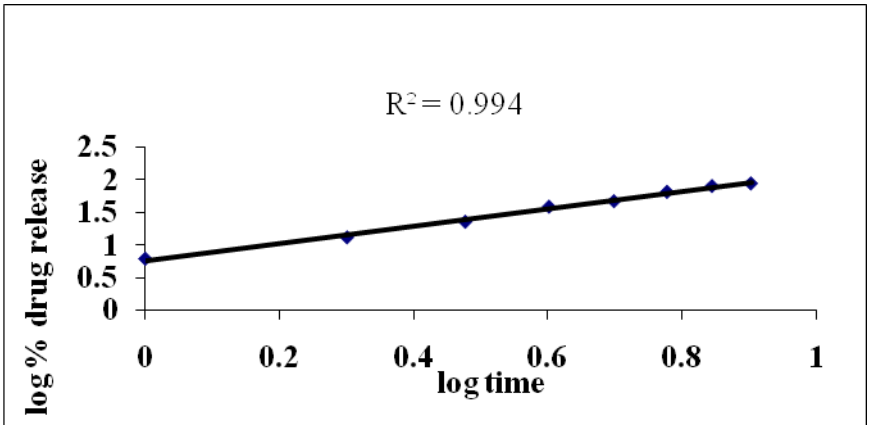


Figure 8.27: Best fit model (Peppas) of formulation F6

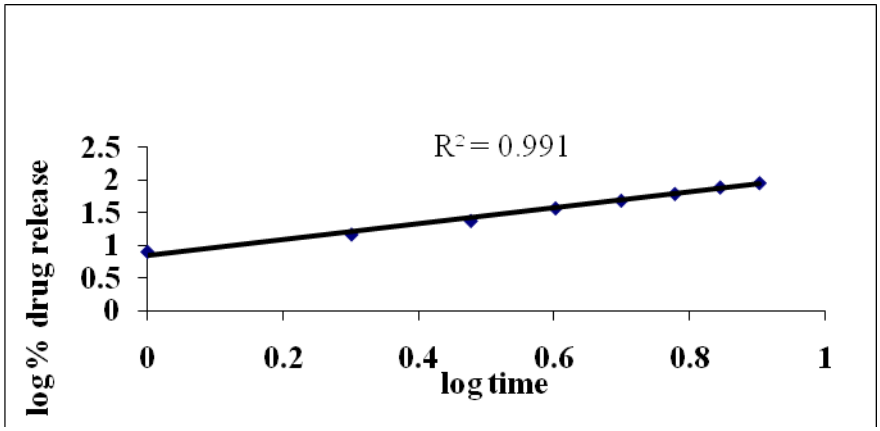


Figure 8.28: Best fit model (Peppas) of formulation F7

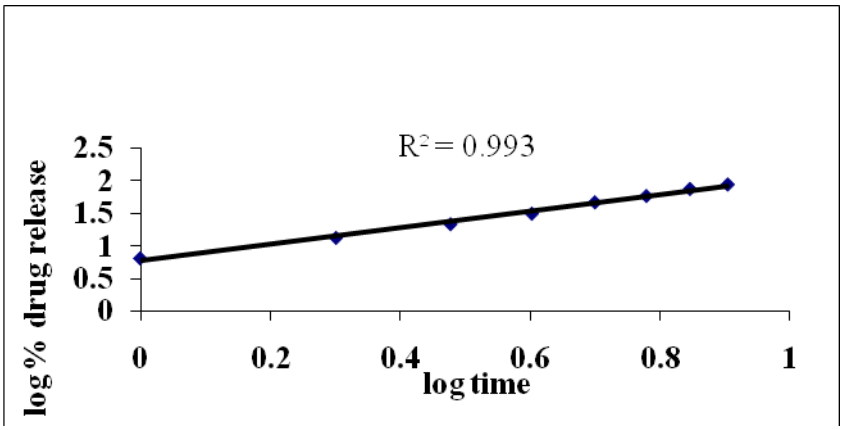


Figure 8.29: Best fit model (Peppas) of formulation F8

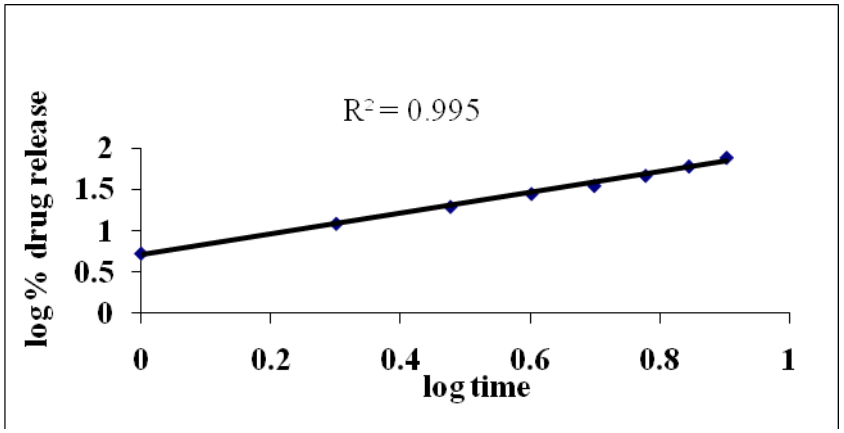


Figure 8.30: Best fit model (Peppas) of formulation F9

To know the kinetics of the best formulations, the release data was treated according to different models. Drug release data of tablets was fitted in peppas equation and found release mechanism to be diffusion.

The results of dissolution data fitted to various drug release kinetic equations. Model was found to be the best fitted in all dissolution profile having higher correlation coefficient followed by the Peppas release equation. The kinetic values obtained from different formulations are tabulated in table 8.22. Optimized formulation F9 shows the Super case II transport Mechanism.

8.4. Stability Study:

After storage the formulation was analyzed for various physical parameters, results are showed in Table 8.23.

Table 8.23: Stability study of best formulation F9.

Characteristic	Initial	1st Month	2nd Month	3rd Month
Hardness (kg/cm^2)*	7.85±0.41	7.67±0.29	7.50±0.00	7.33±0.29
Drug content (%)*	98.90±0.65	98.85±0.76	98.83±1.03	98.69±0.56
In vitro* drug release at 8th hour	78.31±0.38	78.22±0.26	78.18±0.40	78.14±0.38

*All the values are expressed as mean± SE, n=3.

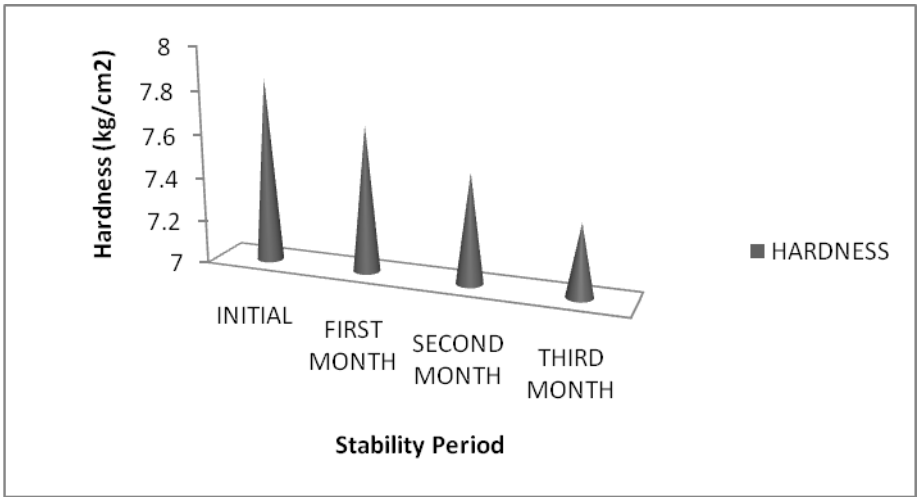


Figure 8.31: Comparisons of Hardness before and after stability period at accelerated temperature (40^0 C ± 2^0 C / 75% RH ± 5%).

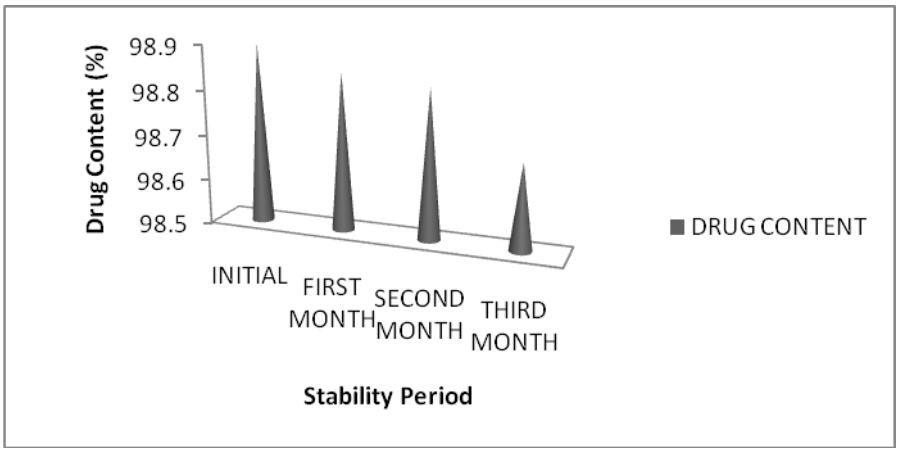


Figure 8.32: Comparisons of drug content before and after stability period at accelerated temperature (40^{0} C ± 2^{0} C / 75% RH ± 5%).

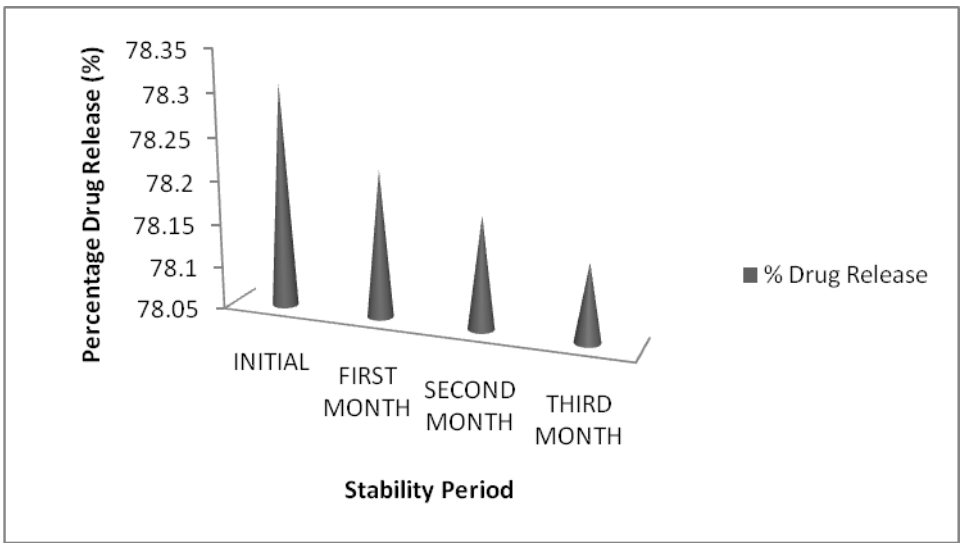


Figure 8.33: Comparisons of *in vitro* Cumulative % drug release before and after stability period at Accelerated temperature (40^{0} C ± 2^{0} C / 75% RH ± 5%)

After 3 months of stability studies at 40^{0} C ± 2^{0} C / 75% RH ± 5%, the results in the table 8.38 given that the optimized formulation F9 had shown satisfactory stability.

Summary & Conclusion

9. SUMMARY AND CONCLUSION

In present investigation an attempt has been made to design and develop Aceclofenac sustained release matrix tablets using HPMC K15M, Carboxy methylcellulose and Xanthan gum, as release retarding polymers. Aceclofenac is widely used as a centrally acting muscle relaxant; therefore have been selected to prepare sustained release dosage forms.

An ideal matrix formulation prepared with different polymers and diluents concentrations should release its content in a sustained profile a reasonable length of time and preferably with Korsmeyer-peppas kinetic.

The active pharmaceutical ingredient Aceclofenac was evaluated for its physical characteristics, analytical profiles and drug polymer compatibility study. The granules were prepared by wet granulation method. The prepared granules were evaluated for Angle of repose, Bulk density, Tapped density and Carr's index. The results obtained were found to be satisfactory and within the specified limits.

After compression parameters like Thickness, Hardness, Weight variation, Friability, content uniformity and *In-Vitro* release studies were evaluated.

Result of the present study demonstrated that hydrophilic polymers could be successfully employed for formulating sustained release matrix tablets of Aceclofenac. The investigated sustained release matrix tablet was capable of maintaining constant plasma concentration upto 8 hours. This can be expected to reduced the frequency of administration and decrease the dose dependent side effects.

The efficacy and safety of Aceclofenac tablet dosage form are expected to offer optimum therapeutic efficacy and improved patient compliance.

In the present study the effect of types and concentration of polymer were studied on *In-Vitro* drug release. It shows that increase in concentration of polymer results in the sustained drug release for 8 hours. The study has revealed that by increasing concentration of polymer, release rate of drug was retarded and results confirmed that the release rate from hydrophilic matrix tablets depends on type and concentration of polymer.

In present studies, matrix formulation containing Xanthan gum 40% is probably showing release up to 78% within 8 hrs.

According to stability study it was found that there was no significant change in hardness, drug content and *in vitro* dissolution of optimized formulation (F9).

Future Prospects

10.FUTURE PROSPECTS

In the present work the sustained release matrix tablets of aceclofenac were formulated using hydrophilic polymers such as HPMC, Carboxy methylcellulose and Xanthan gum by wet granulation method. In this work only physiochemical characterization, formulation and *in-vitro* evaluation matrix tablets of aceclofenac was done. Along with *in-vitro* release study *in-vivo* release behavior of drug is also important. So in future *in-vivo* release study using different models are required to set *the in-vitro in-vivo* correlation which is necessary for development of successful formulation and also long term stability studies are necessary.

Bibliography

11. BIBLIOGRAPHY

1. Anonymous, The Indian Pharmacopoeia. Vol-1, II and III, The Controller of Publication, New Delhi, **2007**, 63-65.
2. Anonymous, The British Pharmacopoeia. Vol-I and II, London: Controller of Her Majesty's Stationary Office, **2009**, 78-82.
3. Anonymous, www.pharmainfo.net
4. Ansel H.C., Allen L.V. and Popovich N.G. Pharmaceutical Dosage Forms and Drug Delivery System. 8th edn., Lippincott Williams and Wilkins, New Delhi, **2009**, 227-274.
5. Anton S.A, Muthu A.K, Panditrao W.B. and Manavalan R. Formulation Development and Evaluation of Ondansetron Hydrochloride Sustained Release Matrix Tablets, *Journal of Pharmaceutical Sciences and Research*, **2009**, 1 (4), 48-54.
6. Aulton M.E. Pharmaceutics: The science of dosage form design, 3rd edn., Churchill Livingstone, New York, **2007**, 355-359,483-498.
7. Bandhalarajan S., Shanmugam S. and Vetrichelvan T. Formulation and Evaluation of Sustained Release Matrix Tablet of Zidovudine Using Different Polymers, *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, **2011**, 2(1), 576-589.
8. Banker G.S. and Rhodes C.T. Modern Pharmaceutics, 4th edn., Marcel Dekker, Inc. New York, **2009**, 167-184.
9. Basak S.C., Jaya Kumar Reddy B.M. and Lucas Mani K.P. Formulation and Release Behavior of Sustained Release Ambroxol Hydrochloride

HPMC Matrix Tablets, *Indian Journal of Pharmaceutical Sciences*, **2006**, 68 (5), 594-598.

10. Brahmankar D.M. and Jaiswal S.B. Biopharmaceutics and Pharmacokinetics A Treatise. 2nd edn., Vallabh Prakashan, New Delhi, **2009**, 397-452.
11. Carstensen J.T. and Rhodes C.T. Drug Stability Principles and Practices, 3rd edn., Marcel Dekker, Inc, New York, **2008**, 415-481.
12. Chandira M., Sandip, Murugantham V., Debjit, Kumundhavalli and Jayakar B. Formulation and Evaluation of Sustained Release Matrix Tablet of Zidovudine, *International Journal of Current Pharmaceutical Research*, **2009**, 1 (1), 14-31.
13. Chein Y.W. Novel Drug Delivery Systems, 2nd edn., Marcel Dekker, Inc, New York, **2002**, 139-196.
14. Fathelrahman A.A. Adam. Design and Evaluation of Prolonged Release Gliclazide Matrix Tablets, **2007**, 1-12.
15. Ganesan V. and Jayachandran D.L. Design and Evaluation of Matrix Tablet of Ambroxol Hydrocloride Using Guargum, *Research Journal of Pharmacy and Technology*, **2008**, 1 (4), 507-512.
16. Ghosh S. and Barik B. Preparation and Evaluation of Aceclofenac Sustained Release Formulation and Compression of Formulated and Marketed Product, *International Journal of Medicine and Medical Science*, **2009**, 1 (9), 375-382.

17. Gothi G.D., Parikh B.N., Patel T.D., Prajapati S.T., Patel D.M. and Patel C.N. Study on Design and Development of Sustained Release Tablet of Metoprolol Succinate, *Journal of Global Pharma Technology*, **2009**, 2 (2), 69-74.
18. Jithan A. Oral Drug Delivery Technology, Pharma Book Syndicate, New York, **2007**, 176-183.
19. Joel A. and Linbird E. Goodman & Gilman's The Pharmacological basis of Therapeutics, 10th edn, Mc Graw Hill Medical, London, **2001**, 708-710.
20. Kabir A.K.L., Biswas B.K. and Shamsur Rouf A.S. Design, Fabrication and Evaluation of Drug Release Kinetics from Aceclofenac Matrix Tablet Using HPMC, *Journal of Pharmaceutical Sciences*, **2009**, 8 (1), 23-30.
21. Keny R.V., Mankame S.A. and Lourenco C.F. Formulation and Evaluation of Once Daily Minocycline Hydrochloride Extended Release Matrix Tablets, *Indian Journal of Pharmaceutical Sciences*, **2009**, 81(5), 295-301.
22. Krishna R. Gupta, Maithili K. Golhar and Rachana R. Joshi. Development and Validation of Spectrophotometric Methods for Determination of Aceclofenac in Tablets, *International Journal of Chem Tech Research*, **2011**, 3 (2), 786-790.
23. Krishnaiah Y.S.R., Satyanarayana V., Bhaskar P., Karthikeyan R.S. and Al-Saiden S.N. Pharmacokinetic Evaluation of Guar Gum Based Three-Layer Matrix Tablets for Oral Controlled Delivery of Highly Soluble Metaprolol Tartrate as a Model Drug, *European Journal of Pharmaceutics and Biopharmaceutics*, **2004**, 58, 697-703.

24. Lachman L., Lieberman H.A. and Kanig J. L. The Theory and Practice of Industrial Pharmacy, 3rd edn., Varghese Publishing House, Mumbai, **1991**, 293-343, 430-439.
25. Lieberman H.A., Lachman L. and Schwartz J.B. Pharmaceutical Dosage Forms: Tablets Vol-I and III, Revised and Expanded, 2nd edn., Marcell Dekker, New York. **1999**, 131-245, 199-213.
26. Manavalan R. and Ramasamy S. Physical Pharmaceutics: Accelerated Stability Testing, 2nd edn., Vignesh Publisher, India, **2001**, 288-299.
27. Manjanna K.M., Sivakumar B. and Pramod Kumar T.M. Formulation of Oral Sustained Release Aceclofenac Sodium Microbeads, *International Journal of Pharma Tech Research*, **2009**, 1 (3), 940-952.
28. Mishra B., Bansal A. and Sankar C. Development and *In-Vitro* Evaluation of Hydrophilic Matrix Tablets of Diltiazem Hydrochloride, *Acta Pharmaceutica Turcica*, **2005**, 47, 115-126.
29. Morkhade D.M. and Joshi S.B. Evaluation of Gum Damar as a Novel Microencapsulating Material for Ibuprofen and Diltiazem Hydrochloride, *Indian Journal of Pharmaceutical Sciences*, **2007**, 69 (2) 263-268.
30. Nasra M.A., El-Massik M.A. and Naggar V.F. Development of Metronidazole Colon Specific Delivery Systems, *Asian Journal of Pharmaceutical Sciences*, **2007**, 2 (1), 18-28.
31. Prema R., Jeevanandham S., Sekar M., Dhachinamoorthi D., Chandra Sekar K.B. and Madhu A. Studies on Fabrication of Baclofen Sustained Release

Matrix Tablets: *In Vitro* Release Pattern Overview, *Res. J. Pharm. Bio. and Che. Sci.*, **2010**, 1(2), 70-77.

32. Radhika P.R., Luqman M. and Borkhataria C.H. Preparation and Evaluation of Aceclofenac Microspheres, *Asian Journal of Pharmaceutics*, **2008**, 2 (4), 252-254.
33. Raghuram Reddy K., Srinivas M. and Srinivas R. Once Daily Sustained Release Matrix Tablets of Nicorandil: Formulation and *In Vitro* Evaluation, *AAPS Pharm science tech.*, **2003**, 4(4), 1-9.
34. Rang A.P., Dale M.M. and Ritter J.M. Pharmacology, 4th edn., Churchill Livingstone, London, **2001**, 226-245.
35. Robinson J.R. and Lee V.L. Controlled Drug Delivery Fundamental and Application, 2nd edn., Revised and Expanded, Marcel Dekker, Inc, New York. **2009**, 337, 373-414.
36. Rowe R.C., Sheskey P.J. and Weller P.J. Handbook of Pharmaceutical Excipients, 4th edn., Pharmaceutical Press and the American Pharmaceutical Association, London, **2003**, 97-99, 108-111, 297-300, 354-357, 641-643, 691-693.
37. Sahoo S.K., Jena M.K., Dhala S. and Barik B. Formulation and Evaluation of Gelatin Micro Pellets of Aceclofenac: Effect of Process Variables on Encapsulation Efficiency, Particle Size and Drug Release, *Indian Journal of Pharmaceutical Sciences*, **2008**, 70 (6), 785-798.

38. Saptarshi D. and Srinivas Rao. Formulation of Evaluation of Metformin Hydrochloride Sustained Release Matrix Tablets, *Journal of Pharmacy Research*, **2010**, 3 (4), 781-784.
39. Sarojini S., Arivazagan D., Manavalan R. and Jayanthi V. Buoyant Sustained Release Tablets Based on Polyethylene Oxide, *International Journal of Pharmacy and Pharmaceutical Sciences*, **2010**, 2 (1), 114-149.
40. Shargel L. and Andrew B.C.Y. Applied Biopharmaceutics and Pharmacokinetics, 5th edn., Singapore, **2005**, 515-548.
41. Sharma A., Shweta S. and Kamal K.J. The Study of Salbutamol Matrix Tablets Using Different Polymers as Release Retarding Agent *The Pharma Research*, **2009**, 1, 15-22.
42. Silverstein R.M. and Webster F.X. Spectrometric Identification of Organic Compounds, 6th edn., Kundli Publishers Ltd., India, **2003,** 79-143.
43. Skoog D.A., Holler F. and Nieman S. Principles of Instrumental Analysis. 5th edn., Thomson Asia Pvt. Limited, Singapore, **1996**, 410-413.
44. Soni T., Nagda C., Gandhi T. and Chotai N.P. Development of Discriminating Method for Dissolution of Aceclofenac Marketed Formulations, *Dissolution Technologies*, **2008**, 31-35.
45. Srinivas M., Krishnan M. and Sreenivasa Reddy M. Chitosan and Enteric Polymer Based Once Daily Sustained Release Tablet of Aceclofenac: *In Vitro* Studies, *American Association Pharmaceutical Sciences*, **2008**, 9 (2), 651-659.
46. Subramanyam C.V.S. Text Book of Physical Pharmaceutics, Vallabh Prakashan. New Delhi, **2009**, 222-228.

47. Suvakanta D., Narasimha M.P., Lilakanta N. and Chowdhry P. Kinetic Modeling on Drug Release from Drug Delivery Systems, *Acta Poloniae Pharmaceutica Drug Research*, **2010**, 67 (3), 217-223.

48. Tabandeh H., Morthazavi S.A. and Guilani T.B. Preparation of Sustained Release Matrix Tablets of Aspirin with Ethylcellulose, Eudragit RS 100 and Eudragit S 100 and Studying the Release Profiles and their Sensitivity to Tablet Hardness, *Indian Journal of Pharmaceutical Research*, **2003**, 201-206.

49. Tripathi K.D. Essential of Medical Pharmacology, 5th edn., Jaypee Brother's Medical Publishers Ltd., **2003**, 167-183.

50. Umesh D.S., Nandha Kishore D.A., Kishore P.B., Vijay B.M. and Digvijay U.A. Formulation, Development and Validation of Sustained Release Tablet of Aceclofenac, *International Journal of Pharmacy and Pharmaceutical Sciences*, **2009**, 1 (2), 74-80.

51. Varshosaz J. and Dehghan Z. Development and Characterization of Buccoadhesive Nifedipine Tablets, *European Journal of Pharmaceutics and Biopharmaceutics*, **2002**, 54, 135-141.

52. Vyas S.P. and Khar R.K. Controlled Drug Delivery, Concepts and Advances, Vallabh Prakashan, 1st edn., New Delhi, **2002**, 1-36, 97-151, 164-170.

53. Yadav I.K., Pratap Singh H., Tiwari P.K., Chandra D., Jaiswal D. and Jain D.A. Formulation, Evaluation and Optimation of Aceclofenac Sustained

Release Matrix Tablets, *International Journal of Pharma Tech Research*, **2010**, 2(1), 592-598.

54. Yeole P.G., Nakhat P.D., Galgate U.C. and Babla I.B. Design and Evaluation of Xanthan Gum-Based Sustained Release Matrix Tablets of Diclofenac Sodium, *Indian Journal of Pharmaceutical Sciences*, **2010**, 68 (2), 185-189.

Annexure

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to me

Maniyarasi M

Acknowledgement receipt of publication charge

We have received 1500Rs as publication charge of your accepted article (JPR_12_528) in JPR

Formulation and evaluation of sustained release matrix tablets of aceclofenac using different polymers.

Your article will be online before 20th March 2012

Before publication we will send proof to you by 105h March 2011

With best regards

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